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THE UNIVERSITY OF ALBERTA

SYNTHETIC METHODS BASED ON FREE RADICAL CYCLIZATION

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A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF Ph.D.

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
FALL 1987

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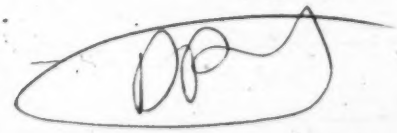

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled SYNTHETIC METHODS BASED ON RADICAL CYCLIZATION.

submitted by DAVID R. CHESHIRE

in partial fulfillment of the requirements for the degree of DOCTOR of PHILOSOPHY.

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1/7/87

To Colin J. Cheshire, Anne M.E. Cheshire,

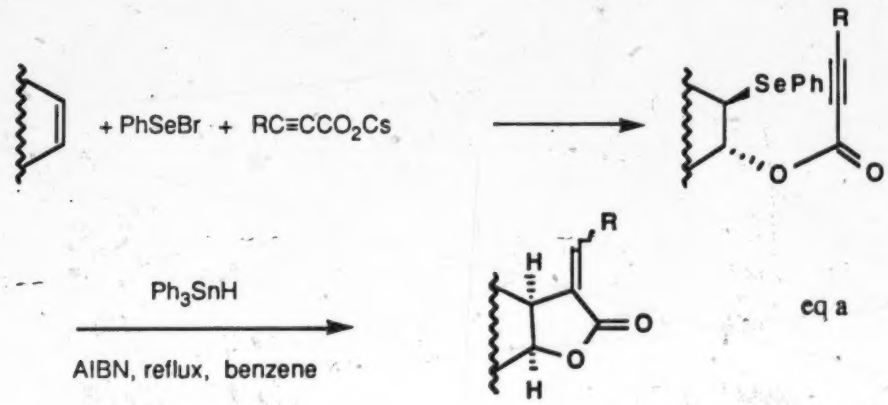
Christopher J. Cheshire and Beatrix L.S. Marshall

ABSTRACT

This thesis contains a brief review of recent developments in the field of radical cyclization and an account of several original contributions to this area.

The new work involved:

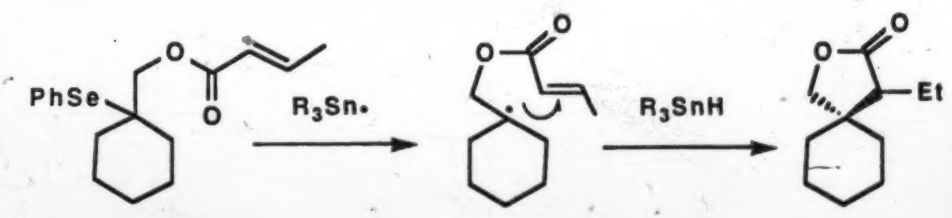
(i) Examination of a method for the synthesis of α-alkylidene butyrolactones as shown, for example, in equation a.



eq a

Cs = Cesium

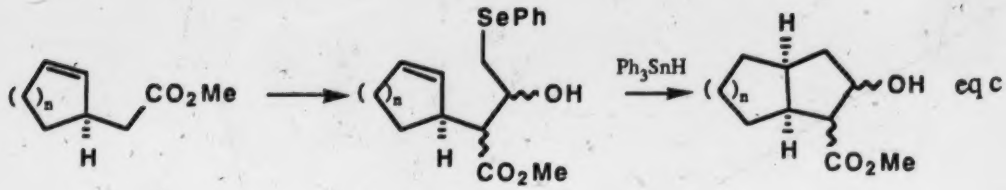
(ii) Development of a method for making spirolactones (equation b).



eq b

R3Sn = trialkylstannyl

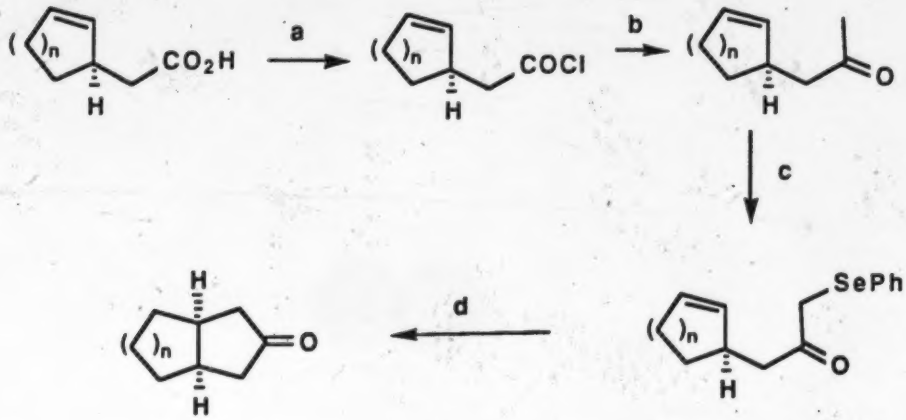
(iii) Development of a route to 5,5 and 5,6 bicyclic compounds (equation c).



eq c

n = 1 or 2

(iv) Discovery that the closure of α-keto radicals-unlike α-keto carbanions-is not subject to a severe kinetic barrier of the type recognized by Baldwin in ionic chemistry. This fact led to the development of a route to cyclopentanones.



a) oxalyl chloride, benzene r.t.b) Me_2CuLi, ethyl ether -78°C. c) i LDA, THF -78°C ii PhSeCl. d) Ph_3SnH, AIBN, benzene reflux. LDA = lithium diisopropylamide.

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I INTRODUCTION

A very important aspect of organic chemistry is the formation of carbon-carbon bonds. Most procedures used for this purpose belong to one of four categories:

1. concerted processes
2. carbanion reactions
3. carbonium ion reactions
4. free radical reactions

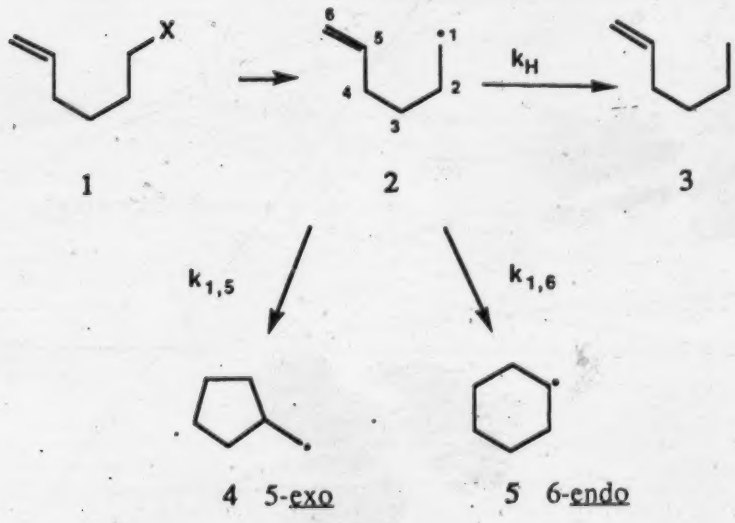
Free radical chemistry offers a number of attractions to the synthetic chemist. It often works under mild and neutral conditions and the reactions are usually not much influenced by the nature of the solvent. One does not have to protect hydroxyl or carbonyl functions as is the case with carbanion chemistry. Furthermore, free radical reactions are not as sensitive to steric factors and thus can be used in the synthesis of sterically congested molecules.

Some of the important features concerning mechanistic investigations and synthetic applications of intramolecular radical cyclizations are summarized below. A number of reviews are available and these give a more extensive treatment of intermolecular and intramolecular radical processes.[1]

Mechanistic Investigations.

The fact that the cyclohexyl radical **5** is more stable than the cyclopentylcarbinyl radical **4** is well established both theoretically[2,3,4] and experimentally.[5,6,7] Based upon this evidence, and the known preference of intermolecular radical additions to occur at the least substituted terminus of a monosubstituted olefin, it might be supposed that radical **2** (derived from a suitable precursor **1**) should cyclize to produce **5** rather than **4** (Scheme 1).

Scheme 1



Understandably, some early workers[8,9] assigned 6-membered ring structures to products obtained from such reactions. In the early nineteen sixties the 5-hexenyl radical was studied more thoroughly with some surprising results.

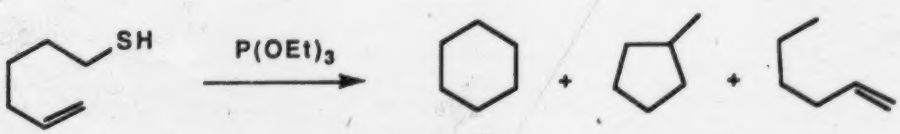
Lamb[4] undertook to investigate the reactions of **2** by generating it from 6-heptenoyl peroxide in toluene at 77°C. Among other products, methyl cyclopentane and cyclohexane were noted in a ratio of 36:1. Lamb tentatively suggested that a reason for this unusual regioselectivity in the cyclization of **2** was that ,at low temperatures in solution, the radical associated with the double bond to form a common intermediate **6** leading to both products.

6

Lamb suggeted that steric requirements for hydrogen abstraction from the solvent determined the product ratio.

Walling and Pearson[10] also studied the 5-hexenyl radical generated from the addition of 6-mercapto-1-hexene to an excess of triethylphosphite containing an initiator [azo-bis-isobutyronitrile (AIBN) at 60°C or di-tert-butyl peroxide (DTBP) at 120°C] (Scheme 2).

Scheme 2

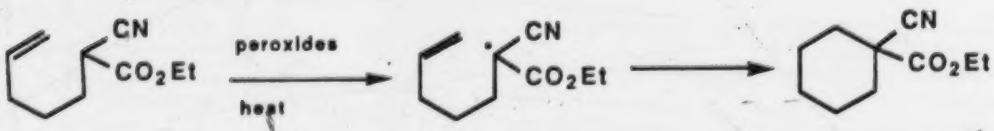


60°C	0%	43%	15%
120°C	3%	5%	13%

Walling and Pearson noted the incongruity in the regioselectivity of the cyclization with the thermodynamic stability of the products.

Brace[11] came across this unusual preference in the free radical addition of 1-iodoperflouropropane to 1,6-heptadiene and subsequent cyclization. He suggested that the result was a manifestation of steric effects in the termination of the radical chain, but it is not obvious how these operate.

At this time Julia[12] was investigating the free radical addition reactions of some unsaturated α-cyano esters (equation1). He observed that the major products were substituted cyclohexanes.[13]



7 eq1

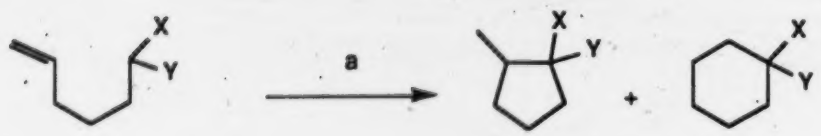
Noting that the radical **7** enjoyed considerable resonance stabilization, he went on to study the effects of variously substituted 5-hexenes (Table 1).[14]

It is clear that there is a gradual change in regioselectivity as the amount of resonance stability that the radical enjoys increases. It had already been noted[4] that, in the case of radical **2**, cyclization is not reversible. Indirect evidence for reversibility of the 5-exo cyclization of the resonance stabilized radicals **7** was obtained by repeating the experiments in solvents known to be better hydrogen donors. Indeed it was found

that when cumene or toluene were used, there was an increase in the amount of **9**. More direct evidence was obtained when the isomeric peresters **11** and **12** were heated in refluxing cyclohexane to yield, in each case, the same product ratio as that obtained from **8** (X = CN, Y = CO_2Et) under identical reaction conditions.

Table 1

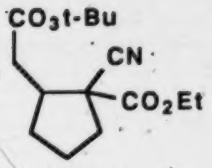
Cyclization of α-cyano esters



8 **9** **10**

X	Y	%	%
H	H	100	0
H	CN	100	0
H	COMe	72	28
H	CO_2Et	56	44
CO_2Et	CO_2Et	70	30
COMe	CO_2Et	50	50
CN	CO_2Et	16	84
CN	CO_2Et[b]	0	100

a = benzoyl peroxide or DTPB in refluxing hexane. **b** ε-methyl group (on double bond)



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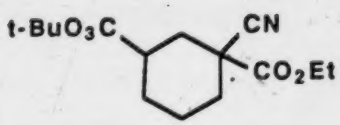


12

This experiment clearly demonstrated that the cyclohexane products were formed as a result of equilibration of the cyclopentylmethyl radical with the thermodynamically more stable cyclohexane radicals prior to hydrogen abstraction from the solvent, i.e. the reaction is under thermodynamic control.

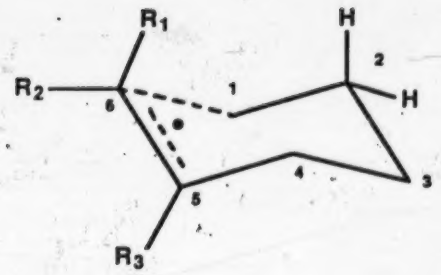
Direct spectroscopic evidence for the cyclization of the 5-hexenyl radical **2** to **4** was also put forward by Kochi and Krusic[15] in the form of EPR spectral data.

Walling[16] first undertook the study of generation of the 5-hexenyl radical **2** from 1-bromo-5-hexene and tributylstannane.[17] It should be noted that the use of stannanes with halides, a contribution by Noltes, Van der Kerk, and Luijten, and especially by Kuivila and Menapace has been of tremendous utility both in mechanistic investigations and synthetic work due to the accessibility of the requisite halides and the hydrogen donating ability of tributylstannane (leading to little or no disproportionation or dimerization). Walling also examined the amount of reduction vs. cyclization (**3** vs. **4** and **5**) that occurred at different hydride concentrations. He found that the rate constant of reduction (k_H) to cyclization (k_C) was ca. 10:1 at 40°C. Thus, as expected, considerably more reduction occurred with higher hydride concentrations. In agreement with Lamb[4], he found that the 5-exo cyclization was irreversible.

In the late sixties, Beckwith[18] suggested that the radical attacked the olefin LUMO at whichever terminus could be approached vertically in the plane of the π system. This, he suggested, explained the ready cyclization of 6-heptenyl systems[19] and the inability of 4-pentenyl systems to undergo intramolecular ring formation.[10]

A number of workers[20] suggested that there was a more favorable entropy of activation ($\Delta S^{\ddagger}$) associated with the formation of the smaller ring. In the late seventies Bischof[21,22] calculated the $\Delta S^{\ddagger}$ for 5-exo cyclization to be 3.3 cal/mol/K more favorable than 6-endo cyclization. This figure was also upheld experimentally. Beckwith[23] determined that at 65°C the enthalpy of activation ($\Delta H^{\ddagger}$) for 5-exo cyclization was 1.7 kcal/mol more favorable than for 6-endo closure and the difference in entropy between the two modes of cyclization was too small to be the dominant factor at ordinary temperatures.

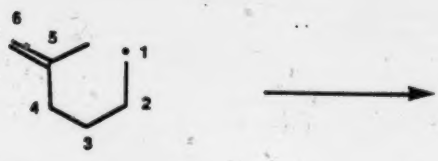
An explanation for the unusual regioselectivity in ring closure of the 5-hexenyl radical **2** was advanced by Julia[24,25] He suggested that there was an unfavorable steric interaction between the pseudoaxial C-2 proton and the syn C-6 proton will destabilize the transition state for 6-endo closure **13**.



13a $R_1=R_2=R_3=H$, **b** $R_2=H$, $R_1=R_3=Me$, **c** $R_1=H$, $R_2=R_3=Me$

This hypothesis was supported by the experimental observation that radical **13b** gave exclusively the 5-exo product whereas radical **13c** gave a mixture of both possible products.[25] The suggestion was that interaction in the 6-endo transition structure between the syn-methyl group and the C-2 pseudo axial proton is important, but the magnitude of the steric interaction cannot be evaluated and it is not clear that the effect in **13a** would be sufficient to account for the observed regioselectivity.

Beckwith and Lawrence[26] studied a number of substituted 5-hexenyl radicals including **14** and **15**. The inhibition of 6-endo closure in **15** can be attributed to a pseudoaxial interaction between the methyl group at C-2 and the syn-C-6 hydrogen. Careful kinetic analysis suggested that the contribution of this interaction was approximately 0.8 kcal/mol.



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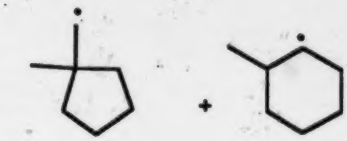

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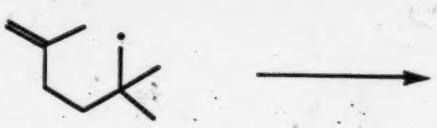

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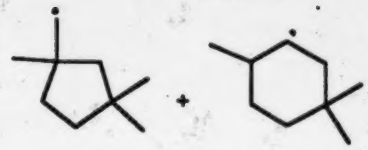
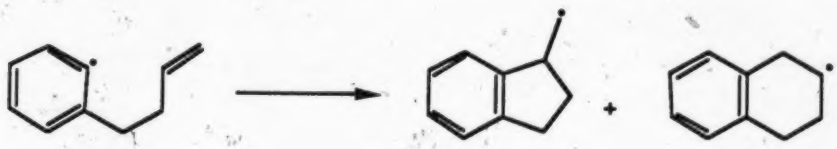


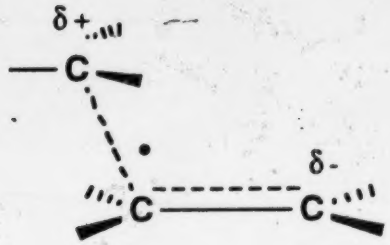
68:32

Since this effect would certainly be less pronounced in the 5-hexenyl radical **2** it cannot account for the observed regioselectivity. Also, aryl radicals of type **16** close exclusively in the 5-exo mode.[27,28] In these molecules there can be no unfavorable steric interaction of the type proposed by Julia.



16 > 99% : < 1%

Beckwith[18,29,30] proposed an explanation based upon stereoelectronic effects. He suggested that the transition state for the intramolecular 6-endo cyclization possessed considerable strain, which outweighed the thermodynamic and steric factors expected to favor formation of the cyclohexane product. At the time, no direct evidence was available for the transition state **17** that he proposed, in which the three atom centers form an obtuse triangle orthogonal to the nodal plane of the π system.



17

Since Beckwith put forward this model for the transition state, a number of theoretical treatments[31] have supported the notion and suggested that the dominant interaction is that between the singly occupied molecular orbital (SOMO) of the radical and the vacant π^* orbital of the double bond. Inspection of molecular models and calculations indicate that this disposition of reactive centers is more easily accommodated in the transition state for the 5-exo cyclization than the 6-endo cyclization. Baldwin[32] also developed a more general set of guidelines governing ring closure reactions for a variety of different systems based on approach vector analysis.

Figure 1

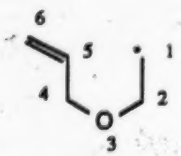
Approach Vector Analysis

trigonal closure

tetrogonal closure

In determining the feasibility of an intramolecular cyclization, he examined the angle α (Figure 1) of approach such that α is equal to the angle between respective bonds in the final product and is maintained throughout the reaction coordinate. The feasibility of the reaction is determined by the ability of the precursor to accommodate the approach vector.

Any change in the structural features of the precursor to cyclization will affect the ease with which the transition state can adopt the required conformation. A clear demonstration of such a change is the cyclization of the 3-oxa-5-hexenyl radical[18,33] **18** which cyclizes far more rapidly than the 5-hexenyl radical and with a greater preference toward the product of 5-exo cyclization.



18

The C-O bond length (1.41 Å) is less than the C-C bond length (1.54 Å) and the C-O-C angle is smaller than the C-C-C angle; thus the C-1-C-5 distance is shorter than in the 5-hexenyl radical **2** and the C-1-C-6 distance longer. These changes permit **18** to better accommodate the transition state for 5-exo cyclization. Radicals **19** and **20** also posses less flexibility in the chain, which greatly increases the difference in strain

energy between the two transition states. Unlike the related carbon analogues, **19** and **20** undergo regioselective ring closure.[27,28]

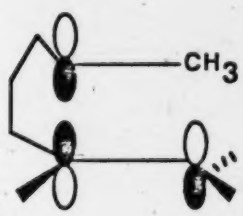
19

20

On thermochemical grounds one would predict that the rates of a set of chemically similar reactions would depend on the relative thermodynamic stability of the products and reactants. Thus, for the 5-hexenyl radical **2**, substitution at C-1 would increase the stability of the reactant and substitution at C-6 would increase the stability of the product. The rates of ring closure should therefore reflect these changes. This is not the case. Substitution at either C-1 or C-6 has little effect on $k_{1,5}$ or $k_{1,6}$.[34] Beckwith suggeste two possible reasons: i) the reaction has an early transition state resulting in little change in hybridization at C-1 or C-6; there is also little transfer of spin density in the transition state and ii) due to the polarity of the transition state **17**, any substitution at C-1 or C-6 would affect the stability of the transition state in the opposite sense to the effect of the substitutions on the stability of the product or the reactant-thus the affects of substitutions are cancelled out. Substitution at C-5 does

increase the amount of cyclohexane product, but only by retarding the rate of 5-exo closure. The effect is quite likely steric in origin. B-strain increases $\Delta H^{\ddagger}$ for the 5-exo cyclization process while the 6-endo cyclization process apparently remains unaffected.

An interesting feature of the 5-exo cyclization of the 1-substituted 5-hexenyl radicals is the preferential formation of cis substituted cyclopentane products.[33a] Beckwith suggested that the stereoselectivity is due to a favorable orbital interaction in the transition state.



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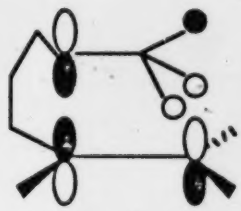

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Radical **21** (leading to cis products) would appear to possess an unfavorable steric interaction. Beckwith suggests that hyperconjugative mixing of the radical SOMO with neighboring σ and σ^* orbitals leads to a modified delocalized orbital of similar symmetry to the vacant π^* orbital of the double bond with which the SOMO is thought to interact (**22**). This gives rise to a favorable interaction outweighing the steric congestion inherent in **21**. He also suggested an alternative explanation which invokes the favorable electrostatic interaction of the dipolar transition state **23**.[1a] *

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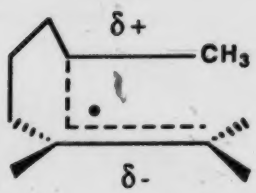
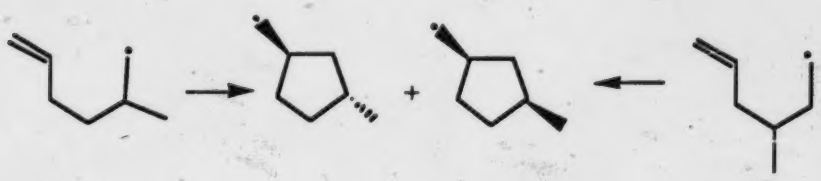
* Pradhan[35] has challenged Beckwith's model, claiming that the SOMO interacts not only with the LUMO of the π-system but also with the HOMO.



23

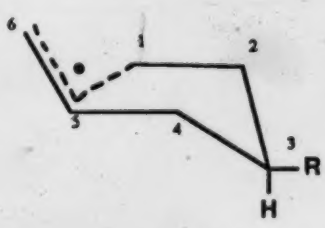
That conformational effects in the transition state are critical to the stereochemical outcome of the reaction is demonstrated by the different product ratios from radicals **24** and **25**.[36]

Radical **24** gives both products, with the <u>trans</u> isomer **26** predominating, whereas **25** gives predominantly the <u>cis</u> isomer **27**.

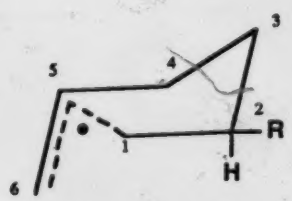


24 **26** **27** **25**

Theoretical calculations[31] suggest that the transition state for 5-<u>exo</u> cyclization is best represented by a chair-like conformer **28**.



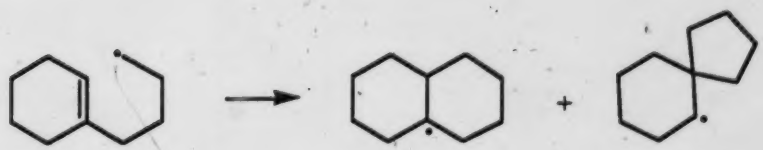
28



29

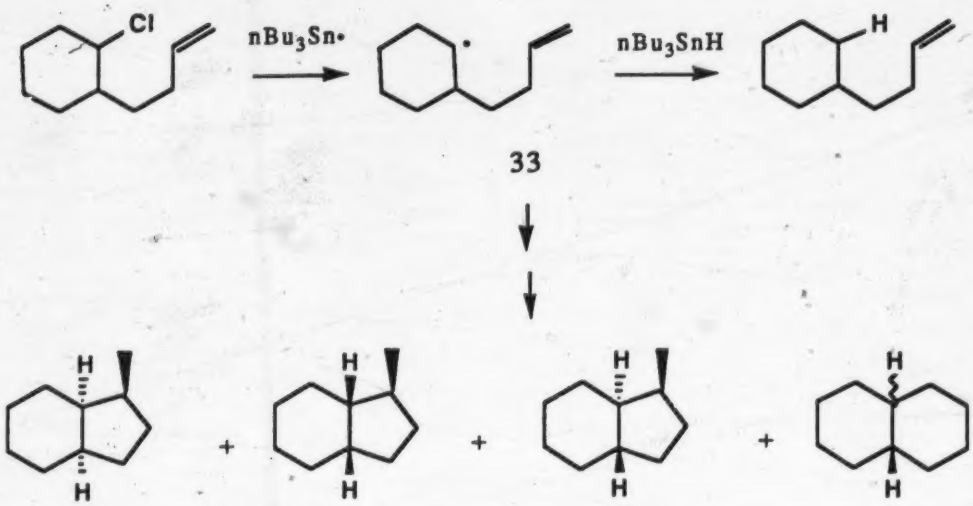
Any substituent at C-3 will prefer to occupy a pseudo-equatorial position (**28**) which leads to the formation of the cis product **27**. Similarly, any substituent at C-2 or C-4 will also prefer a pseudo-equatorial disposition in the transition state (**29**) and thus produce the trans isomer **26** preferentially. Presumably, a more bulky substituent at any of these positions will augment the selectivity.

The study of cyclic radicals in the formation of bicyclic systems is more complex. Beckwith[18] studied the 4-(cyclohexenyl)butyl radical **30**. Both **31** and **32** were formed, with **32** predominating, despite the higher thermodynamic stability of the radical **31**. The value of $k_{1,5}$ was considerably smaller than with the 5-hexenyl radical **2** but, since radical **30** is regarded as a C-5 substituted 5-hexenyl radical, this observation is not surprising.



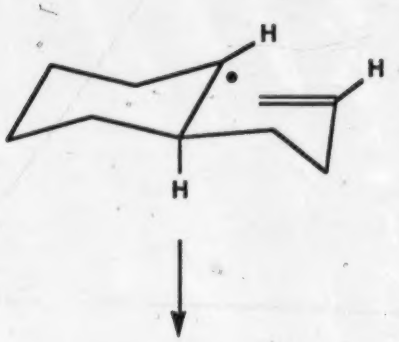
30 **31** **32**

The stereoselectivity of the 4-(cyclohexyl)butenyl radical **33** is a little more involved.[37a]

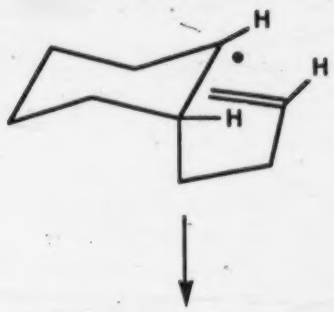


34 (56.3%) + **35** (15.9%) + **36** (3.7%) + **37** (2.0%)

Radical **33** can be viewed formally as a 1,2-disubstituted-5-hexenyl radical and thus one would expect **36** to be the major product, and not **34**. The ring must therefore impose steric constraints on the transition state that do not apply in the simple acyclic systems. Beckwith suggests that stereoelectronic factors determine that the butenyl side chain occupies a pseudo axial position in the transition state thereby allowing better interaction between the radical SOMO and the vacant π^* orbital. The cyclopentyl analogue of **33** behaves in a similar manner.[37b]



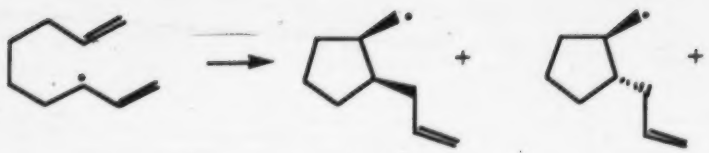
36



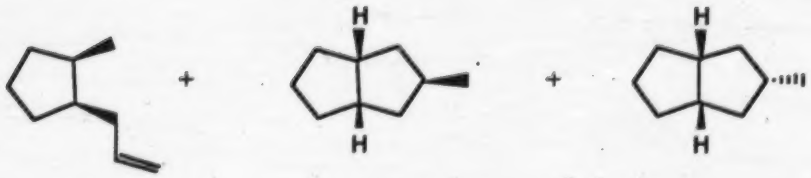
34

This conformational preference leads to the formation of **34** as the major product. Compound **36** arises from the transition state where the side chain is disposed equatorially. Small amounts of cis- and trans-decalin **37** are also formed. Pradhan[35] suggests that Beckwith's explanation assumes the two lobes of the radical SOMO have equal dimensions on both sides of the nodal plane. Pradhan states that the SOMO of radical **33** is extended more in an axial direction (above the plane of the cyclohexyl ring); favorable interactions between the SOMO and the appropriate π orbitals can set in at a shorter distance with the butenyl side chain disposed in a pseudo equatorial position, thus ensuring a cis-fused product.

Another interesting example is the allylic radical which gives the cyclic radical **38** as the major product of it's first cyclization. Radical **38** maybe viewed as a 2,3-disubstituted 5-hexenyl radical, the two substituents would be expected to offset each other's effect upon the stereoselectivity of the reaction. Thus **38** yields **40** and **41** with a slight preference for the endo isomer **40**.

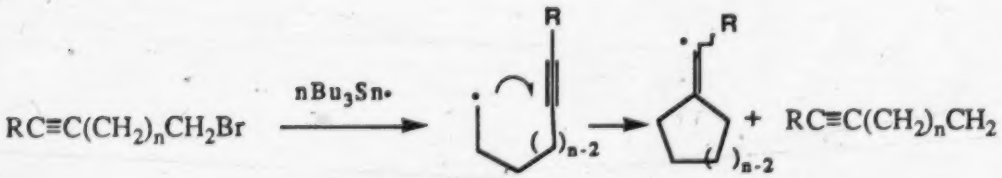


38 (59.6%)

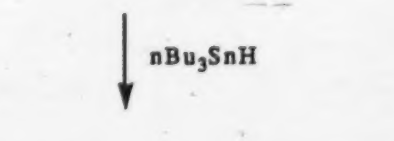


39 (1.6%) 40 (35%) 41 (23%)

In the late sixties Crandall[38] first investigated the properties of alkynyl radicals 42 .



42



43 44

The acetylenic halide was refluxed with tributylstannane in benzene. The results are outlined in Table 2.

Table 2

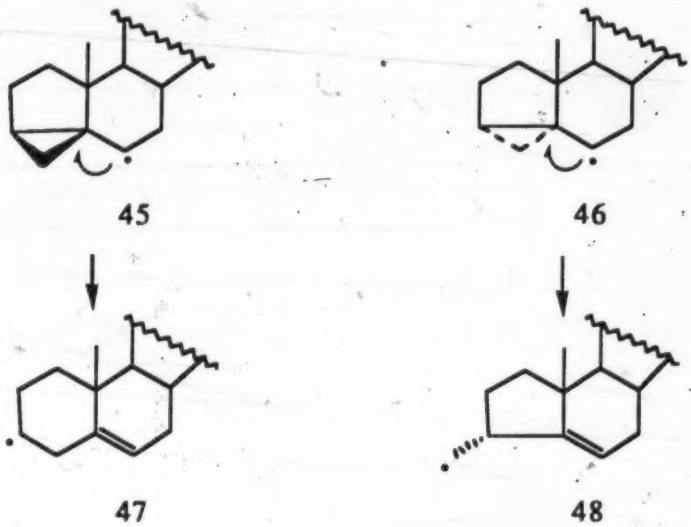
Cyclization of Alkynyl radicals.

42		43	44
n	R	%	%
1	Ph	99	0
2	Ph	99	0
3	Ph	0	99
4	Ph	50	50
4	C_5H_{11}	98	0

He concluded that the regioselectivity was comparable to that found for the 5-hexenyl radical **2** . The linearity of the acetylenic carbons affects the flexibility of the transition state and leads to regioselective 5-exo cyclization, of **42** but at a slower rate than for the 5-hexenyl radical **2**[1a] Values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ become increasingly unfavorable in going from 5-hexynyl to 6-heptynyl to 7-octynyl. The regioselectivity of hydrogen abstraction by the intermediate vinyl radical (R = Ph and R = OEt) has been investigated by Simamura.[39]

In general the process of free radical addition is reversible but at normal temperatures the equilibrium lies heavily towards addition. The reverse process, β-

scission, occurs only when there is sufficient incentive, for example the relief of ring strain. Free radical addition is known to be under stereoelectronic control and thus one would expect β-scission also to be susceptible to stereoelectronic effects. A good demonstration of this is the study of two isomeric steroid radicals **45** and **46**.[40]



45 **46**

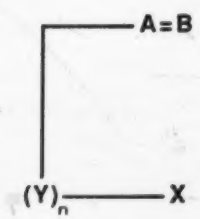
47 **48**

Species **46** rearranges cleanly to give **48** and no cholest-5-ene (derived from **47**). In each case the cyclopropyl bond which undergoes scission is the one which lies closest to the plane accommodating the radical SOMO. Cyclopropyl and cyclobutyl carbinyl radicals undergo ring cleavage under mild thermal conditions, presumably because the radical center can rotate freely. Cyclopropyl radical scission to give the allyl radical, even though highly exothermic, is a slow process under similar conditions. Beckwith suggests the mandatory overlap of the radical SOMO with a suitable σ bond is more difficult to attain in the cyclopropyl radical. Larger ring

cycloalkyl radicals do possess the necessary conformational flexibility to allow orbital overlap but lack the necessary driving force inherent in lower homologues. There are many examples of reactions which follow the less exothermic pathway, a result which can be rationalized by invoking stereoelectronic effects.

In 1980, Beckwith[41] published a number of guidelines which, when used in conjunction with thermochemical criteria for radical processes, allow rationalization of the outcome of certain radical processes. His suggestions are :

i) Intramolecular addition under kinetic control in lower ($n < 5$) alkenyl and alkynyl radicals and related species (X = C,N,O ; AB = CO or CN) occurs preferentially in the exo mode (**49** to **50**).



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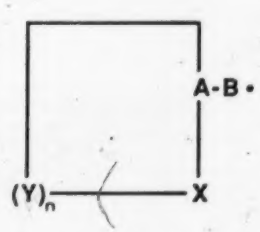

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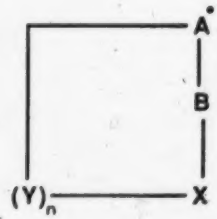
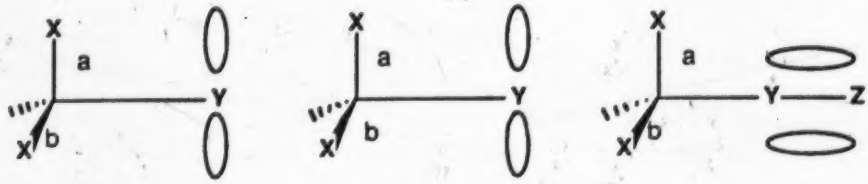


51

ii) Substituents on an olefinic bond disfavor homolytic addition at the substituted position and retard the rate of conversion of **49** to **50**.

iii) Homolytic cleavage is favored when the cleaving bond lies close to the plane of an adjacent radical SOMO or of an adjacent filled non-bonding orbital.



52 53 54

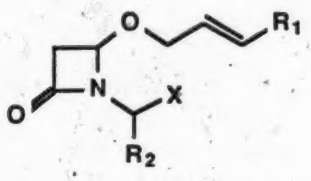
This guideline indicates that in systems such as **52**, **53** and **54** scission of bond **a** will occur more rapidly than scission of bond **b** and so <u>exo</u> radicals **50** will undergo scission more rapidly than the product of <u>endo</u> closure (radical **51**).

iv) 5-Exo ring closure of substitued 5-hexenyl radicals **2** can be stereoselective. Systems with substituents at C-1 or C-3 afford mainly <u>cis</u>-disubstituted products, whereas 2- or 4-substituted systems afford mainly <u>trans</u> products.

Beckwith[42] has also compared the relationship between the rate of cyclization, the regiochemistry and stereochemistry of closure, and the strain energy for the respective transition states (calculated using Allinger's MM2 method). The theoretical and experimental results show good agreement.

<u>Synthetic applications.</u>

The application of radical cyclization to the synthesis of β-lactam antibiotics was first explored by Bachi.[43] He realized that the mild reaction conditions for radical cyclization would be ideal for preparation of the sensitive β-lactam system. He synthesized a number of substrates of type **55** .



55 a X=Cl, R_1=R_2=H

b X=Cl, R_1=H, R_2=CO_2tBu

c X=Cl, R_1=CO_2Me, R_2=CO_2tBu

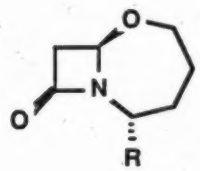
d X=Cl, R_1=Ph, R_2=CO_2tBu

e X=SePh, R_1=R_2=H

f X=SPh, R_1=R_2=H

g X=

When either compound **55a** or **55b** was dissolved in benzene and refluxed for 44 h with tributylstannane the cyclized product **56a** (34%) or **56b** (47%) was isolated, along with the reduced β-lactam **57a** (31%) or **57b** (32%).



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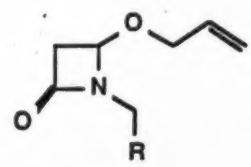
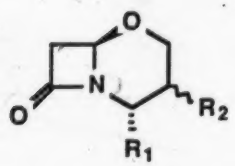


57

a R = H ; **b** R=CO_2tBu

He observed the unusual occurrence of 7-endo cyclization: products from 6-exo cyclization were absent. This result is quite different from the behavior of the 6-heptenyl radical where the 6-exo mode of cyclization is preferred.[23] With **55c** and **55d** the 6-exo cyclization products **58c** and **58d** predominated.

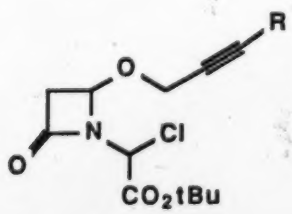


58 **c** R_1=CO_2tBu, R_2=CH_2CO_2Me

d R_1=CO_2tBu, R_2=CH_2Ph

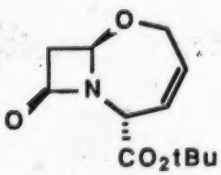
It was obvious that substituents on the double bond affected the preferred mode of cyclization and thus some selectivity was possible. Bachi also studied the N-(phenylselenenyl)alkyl and N-(thiophenyl)alkyl β-lactams **55e** and **55f** (prepared from the N-chloroalkyl β-lactams under phase transfer conditions with bezeneselenol and benzenethiol) as the N-chloroalkyl lactams were unstable and had to be used directly without purification. The two substrates gave product ratios similar to the N-chloroalkyl β-lactams, an observation which indicated the intermediacy of a common radical species **55g**.

A more thorough investigation by Bachi appeared later[44] and the properties of the propargyl β-lactams **59** were discussed.

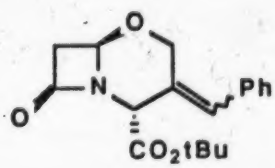


59a R = H, **b** R = Ph

With **59a**, the endo mode of cyclization was preferred, leading to **60**. When the terminal position was substituted, as in **59b**, the exo mode of cyclization dominated, yielding **61**.



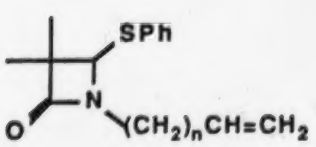
60



61

This regiochemistry was dependent on the the substitution of the unsaturated portion of the precursor and allowed selective entry into the 1-oxahomocephams (**56**) and the 1-oxacephams (**58**) and their didehydro derivatives (**60** and **61** respectively).

Beckwith[45] also investigated the synthesis of bicyclic β-lactams. As expected, **62a** gave no cyclization products; only the reduced material **63a** was formed on treatment with tributylstannane. Under similar conditions, compounds **62b** and **62c** gave mixtures of cyclized products **64b** and **64c**, respectively, along with the corresponding reduction products **63b** and **63c**.



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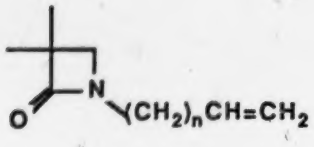

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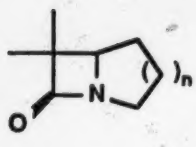
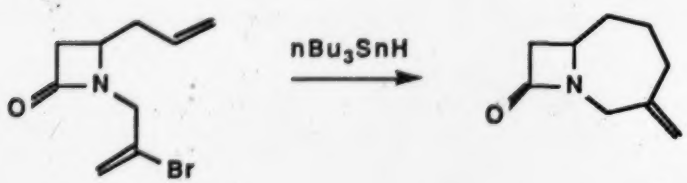


64

a n = 1, b n = 2, c n = 3

No products from 5-or 6-exo cyclization were observed. Beckwith suggested that the selectivity reflected "the strain in the exo transition structure engendered by the four membered ring".

Recently, Knight[46] has reported on the use of a vinyl radical cyclization for the preparation of carbapenams and carbacephams. He first noted that **65** gave exclusive 7-endo ring closure (equation 2).

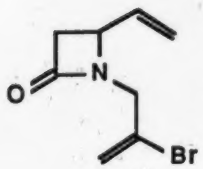


77 % eq 2

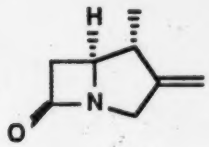
65

Therefore, he turned his attention to the lower homologue **66** in the hope of obtaining 6-endo closure to give the carbacepham skeleton. Under photolytic conditions [n-Bu_3SnH , AIBN (cat), *hv*], **66** yielded the 1α-methylcarbapenam **67** along with the β-lactam derived from simple reduction of the intermediate radical. In contrast to this result, high dilution cyclization, again under photolytic conditions, gave

the cabacepham **68** (30%) which was also the main product (58%) under thermal reaction conditions [n-Bu_3SnH , AIBN (cat), reflux benzene]. The formation of **68** is understandable in terms of the characteristic ring expansion often seen in the closure of vinyl radicals.[47]



66



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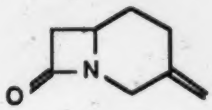
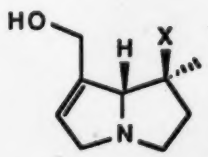


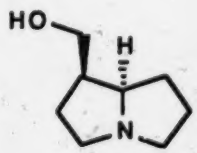
68

Thus, Knight's work shows that the cyclization of substrates such as **66** is tunable to afford either the 1α-methylcarbapenam **67** or the carbacepham **68.**

Hart has used radical cyclization to synthesize a number of alkaloids, including supinidine **69a**,[48] heliotridine **69b**[49] and isoretronecanol **70**.[50]

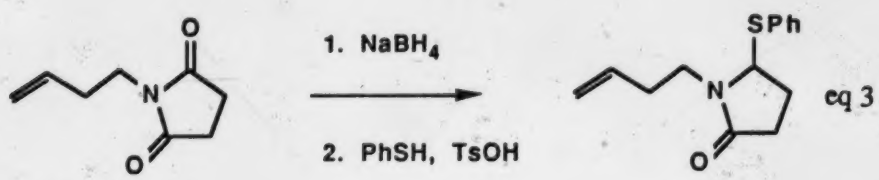


69 a X=H, **b** X=OH



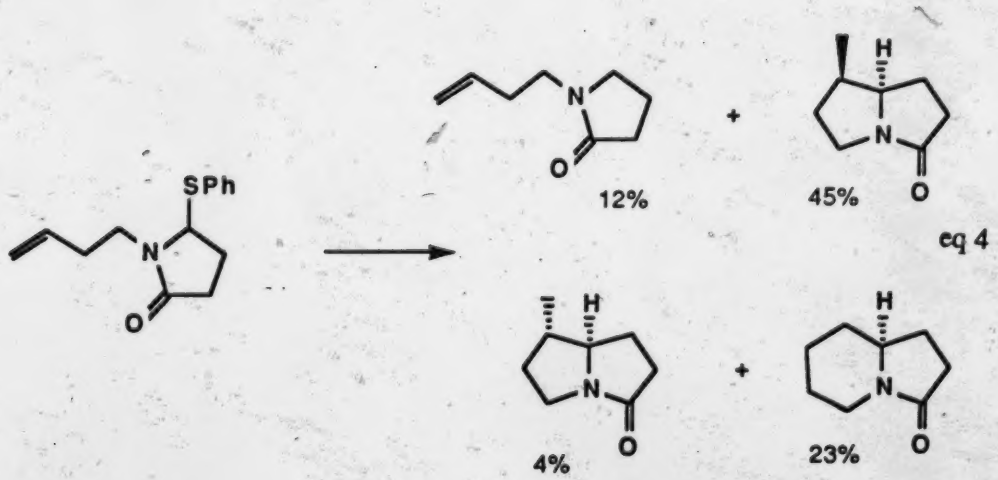
70

In preliminary work,[48] he studied the N-alkenyl butyroamides **71**, easily prepared (equation 3) by Mitsunobu reaction between the appropriate homoallylic alcohol and succinimide. Reduction of the adduct with sodium borohydride and treatment of the resulting carbinolamide (without isolation) with thiophenol under acidic conditions efficiently afforded the substrate required for cyclization.

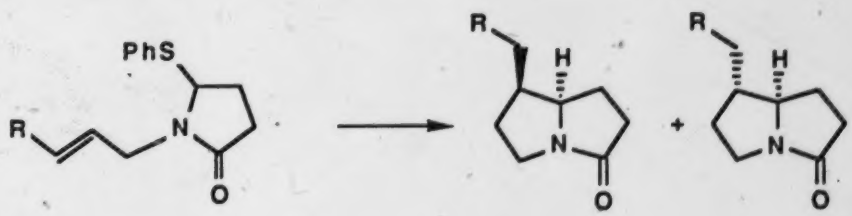


71

When **71** was treated with tributylstannane, a number of products were obtained (equation 4).



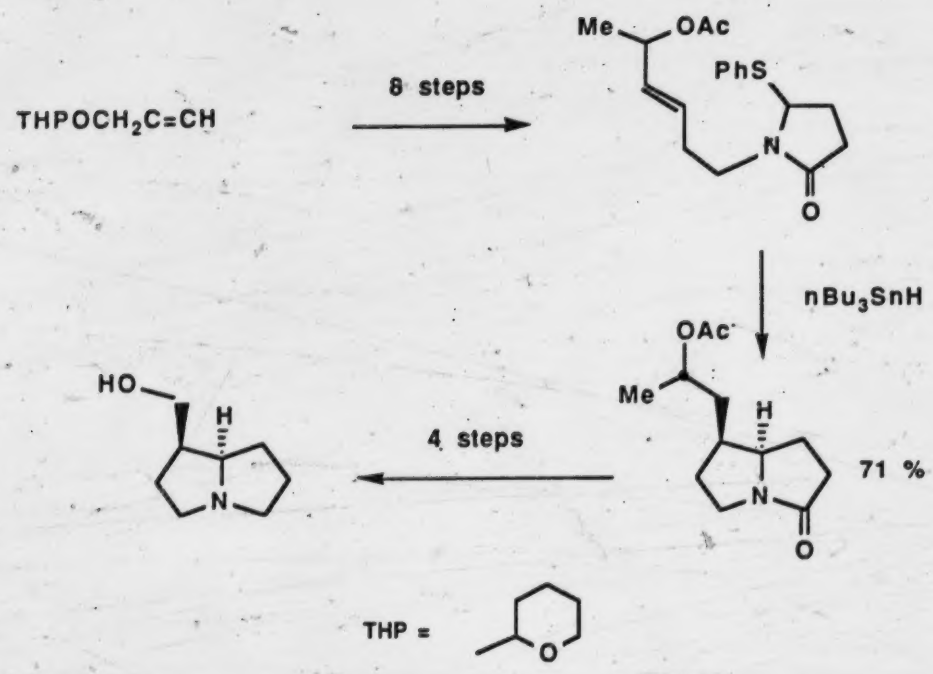
Unlike the β-lactam analogues, pyrollidinyl radicals displayed a preference for the 5-exo mode of cyclization. Further study indicated that the products of cyclization were not the result of thermodynamic control. Hart suggested that the wider C-N-C bond angle was responsible for the decreased exo/endo selectivity compared to that found in the case of the 5-hexenyl radical **2**. The high diastereoselectivity of the reaction was not surprising.[37b] Hart also demonstrated[50] that the positioning of an appropriate electron withdrawing group at the terminus of the double bond increased the rate of the 5-exo cyclization such that the reactions were of synthetic use.



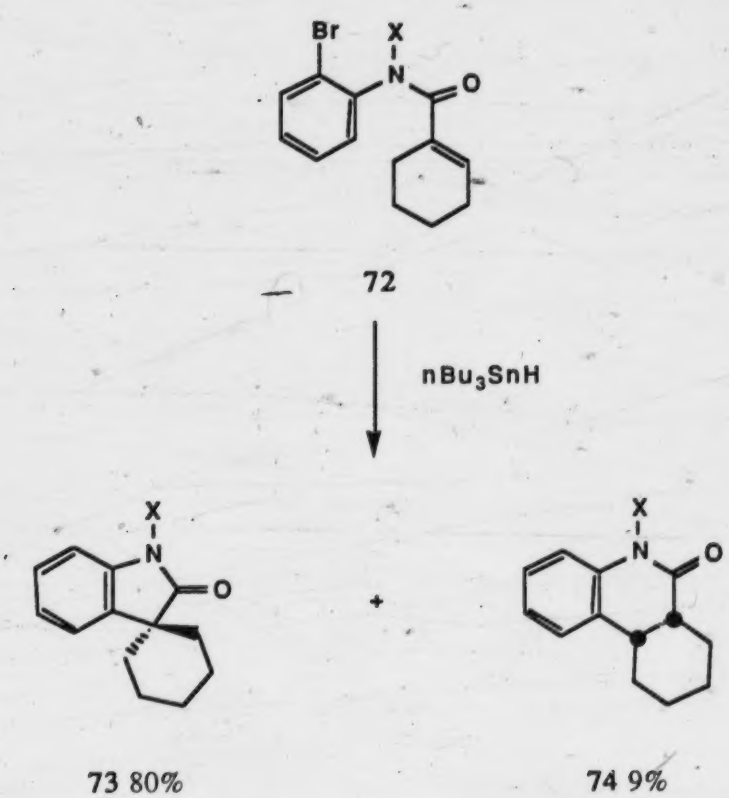
		β		α
R = CN	85%	β:α	9:1	
R = CO_2tBu	82%	β:α	9:1	

Illustrative of the applicability of this approach is the synthesis of isoretronecanol (Scheme 3) which was accomplished in an overall yield of 11% from the tetrahydropyranyl ether of 2-propyn-1-ol.

Scheme 3



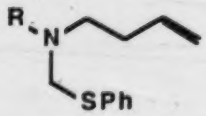
Jones[51] recently developed a mild synthesis of 3-substituted 2-oxindoles. He was particularly interested in the synthesis of the 3-spiro-2-oxindole system as part of an effort towards the synthesis of the Gelsemium alkaloids. For example, **72** could be cyclized under thermal conditions [nBu3SnH, AIBN (cat), reflux benzene] to give **73** along with the product of 6-endo cyclization, **74**.



73 80% 74 9%

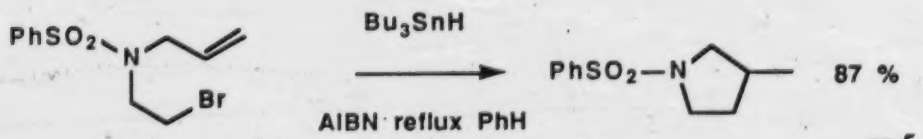
Jones found that it was necessary to protect the nitrogen prior to cyclization, presumably because amines are known to react with trialkyl stannanes. He found that the use of the bulky SEM ($Me_3SiCH_2CH_2OCH_2$-) protecting group increased the regioselectivity in favor of the 2-oxindole products.

Padwa[52] investigated a procedure for the synthesis of the pyrollidine ring system. His initial attempts were unsuccessful. Treatment of **75a** under thermal conditions [nBu3SnH, AIBN (cat), reflux benzene] resulted in complete reduction and no cyclization.



75 a R = CH_2Ph, b R = SO_2Ph

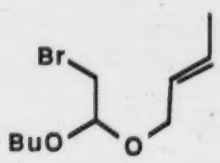
He attributed this result to stabilization of the radical by the adjacent nitrogen. In support of this interpretation, substrate **75b** was found to undergo competitive reduction and cyclization (36%). If the radical center was remote from the nitrogen, as in **76**, the problem was resolved and cyclization proceeded in a synthetically useful yield to produce **77** (equation 5).



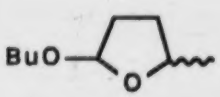
76 **77** eq 5

Padwa then went on to study the effect of substitution on the double bond and found that such as **76** radicals displayed a higher regioselectivity for 5-exo cyclization than the corresponding substituted 5-hexenyl radicals. He attributed this to the fact that the C-N bond length is shorter than the C-C bond length and the C-N-C angle is smaller than the C-C-C bond angle. This 'tightening' of the transition structure presumably increases the strain in a 6-exo transition state.

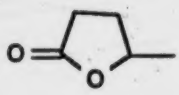
In 1982 Ueno[53] reported the synthesis of 2-alkoxytetrahydrofurans and γ-lactones via radical cyclization. He found that bromoacetal **78** cyclized to the corresponding acetal **79** in 59% yield when treated with tributylstannane in refluxing benzene. The bromoacetals were derived from the allylic alcohol and butyl vinyl ether in the presence of N-bromosuccinimide.



78



79

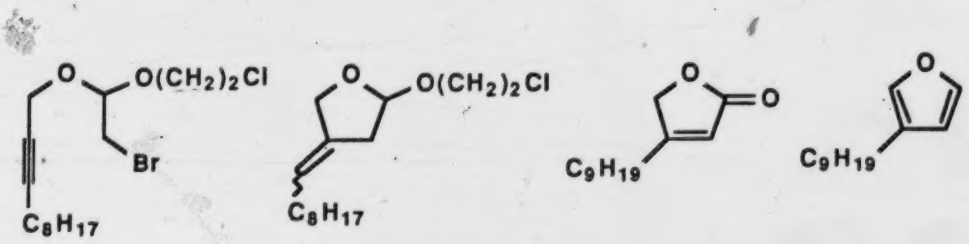


80

The moderate yield in the cyclization was attributed to the difficulty in isolation of the acetals from the residual organotin species. In order to circumvent this problem, Ueno used a polymer supported tin catalyst. Thus, cyclization was effected by irradiation of a solution of **78**, polymer catalyst (0.1 equiv.) and sodium borohydride (1.5 equiv.), in degassed benzene-ethanol at room temperature for 30 min. Filtration of the crude reaction product to remove the polymer catalyst gave the acetal **79** free of organotin impurities in 89% yield.

Ueno found that the catalyst could be used five times without significant loss of reactivity. Oxidation of the acetal using Jones reagent yielded the γ-lactone **80** in 79% yield. Ueno[54] has since made more contributions this area.

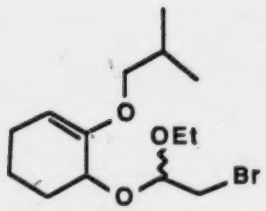
Stork[55] reported the use of bromoacetals as substrates for cyclization. He demonstrated the versatility of this methodology in the synthesis of 3-substituted furans and butenolides. For example, the cyclic acetal **82**, derived from **81**, can be converted into the butenolide **83** (deprotection of **82** and oxidation with Jones reagent) or into the furan **84** (action of acid on **82**).



81 **82** **83** **84**

The combination of readily available starting materials (allylic alcohols and vinyl ethers) and the directness contribute to the appeal of this approach.

Pattenden[56] has applied the cyclization of these α-halo acetals to the synthesis of β-alkoxy-γ-lactones, a structural unit found in a number of interesting natural products with varied biological activity. Bromoacetal **85** was derived from the reduction of 2-(2-methylpropoxy)cyclohexene-1-one with diisobutylaluminum hydride and subsequent reaction of the allylic alcohol with 1,2-dibromoethyl ether. Treatment with tributylstannane yielded the cyclic acetal ether **86** in 91% yield.



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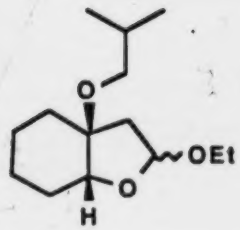
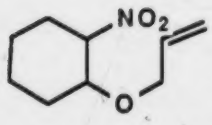


86

Oxidation of **86** with Jones reagent furnished the γ-lactone in 70% yield. In all the cases investigated, only one isomer was forme. This was assigned a cis-ring-fusion due the increased strain inherent in trans-fused γ-lactones.

Ono[57] has reported a method for the synthesis of furans using the chemistry of nitro olefins. For example, Michael addition of allyl alcohol to 1-nitrocyclohexene yields **87**. α-Acetoxymethylation with aqueous formaldehyde in the presence of acetic anhydride and pyridine yields **88**. Treatment of **88** with tributylstannane in refluxing benzene gives a mixture of isomeric furans **89** in 74% yield. As with the cyclization of similar substrates, the formation of a quaternary center does not hinder the reaction.



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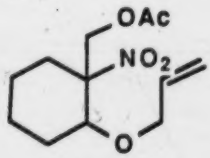

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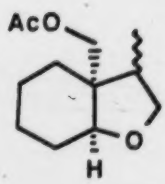
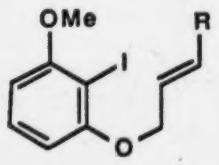


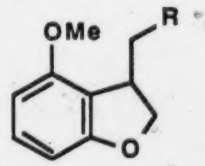
89

Snieckus[58] has synthesized dihydrobenzofurans such as **91** using 2-iodo allyl ethers **90** derived from orthometallation procedures. The combination of the two

synthetic methods—orthometallation and radical cyclization—provides a expedient route to molecules which are difficult to obtain by more classical chemistry. Cyclization was effected with tributylstannane in refluxing benzene to yield various dihydrobenzofurans **91** in good yield.

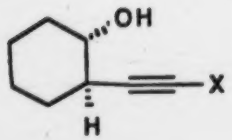


90

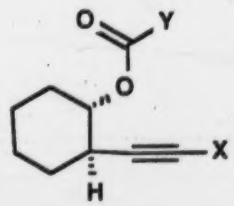


91

The synthesis of α-alkylidene-γ-lactones has recently been reported by Bachi.[59] Treatment of an epoxide with a lithium acetylide in the presence of boron trifluoride etherate yields the 3-alkyn-1-ols **92**. Reaction with phosgene, and then benzeneselenol in pyridine, yields the (phenylseleno)carbonates **93**.

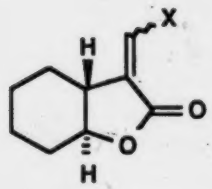


92 X = SiMe3, Ph



93 X = SiMe3, Ph, Y = SePh

94 X = SiMe3, Ph, Y =

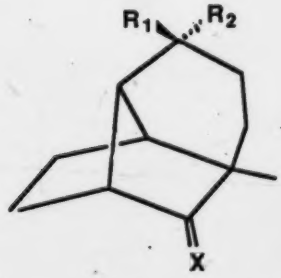


95 X = $SiMe_3$, Ph

Reaction of the carbonates with tributylstannane yields the α-alkylidene-γ-lactones **95** in excellent yield. The radical **94** does not undergo reduction or β-elimination to any significant extent.

Two of the earliest examples of the use of radical cyclization for synthesis were reported in the late seventies by Bakuzis[60] and Büchi.[61]

Bakuzis reported the total synthesis of two terpenoid natural products, sativene **96a** and copacamphene **96b**.

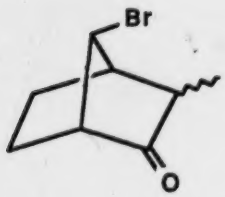


96 X = CH_2 **a** R_1 = Me_2CH, R_2 = H ; **b** R_1 = H, R_2 = Me_2CH

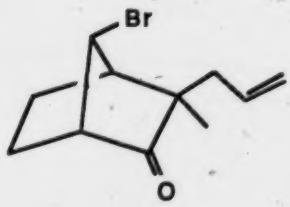
100 X = O **a** R_1 = Me_2CH, R_2 = H ; **b** R_1 = H, R_2 = Me_2CH

The approach that Bakuzis adopted was certainly ahead of its time. Alkylation of the magnesium enolate of syn-7-bromobicyclo(2.2.1)heptan-2-one **97** with 1-

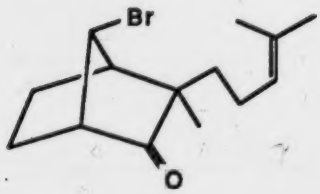
bromo-2-propene yielded **98** and its C-3 epimer in a 4:1 ratio, along with some O-alkylated material.



97



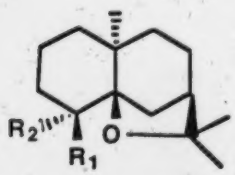
98



99

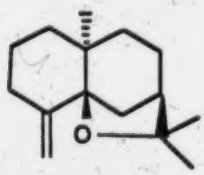
Reaction of **98** with thiophenol (AIBN—initiated) gave the alkyl sulfide arising from addition of PhS to the terminus of the olefin. Treatment of the sulfide with N-chlorosuccinimide followed by hydrolysis gave an aldehyde which was immediately reacted with the Wittig reagent $Ph_3P{=}CH(Me)_2$ to yield **99**. Irradiation (257 nm) of **99** in benzene at 36°C in the presence of tributylstannane (initiated with tert-butylperbenzoate) gave a 3:2 mixture of norsativone **100a** and copacamphenilone **100b** in a 62% yield. These ketones were then transformed (by published procedures) to sativene **96a** and copacamphene **96b**

Büchi reported the synthesis of (±)-dihydroagarofuran **101a**, a major odorous constituent of galbanum.



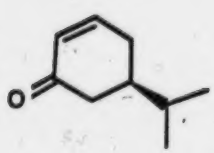
101a R_1 = H, R_2 = Me

b R_1 = Me, R_2 = H

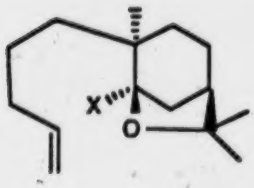


102

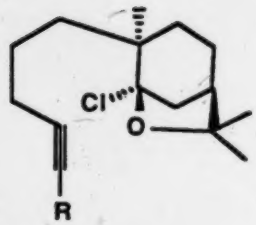
Previously reported syntheses were flawed because hydrogenation of β-agarofuran **102** under a variety of conditions lead to a mixture of isomers (favoring isodihydroagarofuran **101b**). Also products resulting from the cleavage of the tetrahydrofuran portion of the molecule were observed. The cyclization precursor **103a** was synthesized in 5 steps from (-)-carvone **104**. Treatment of **103a** with tributylstannane with a catalytic amount of AIBN in refluxing cyclohexane lead to a 7:3 mixture of epimers at C-4, with isodihydroagarofuran, **101b**, as the major component. The isomer ratio, as expected, did not vary with a change in the concentration of tin hydride but the amount of reduced material produced was a function of the hydride concentration.



104



103a X = Cl, b X = H



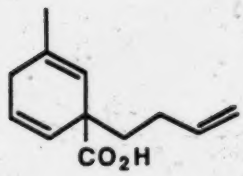
105a R = H

b R = $SiMe_3$

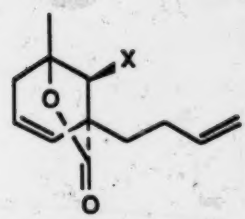
Buchi found that reaction of **105a** under similar conditions lead to a complex mixture of high molecular weight products, presumably arising from intermolecular addition of the stannane to the acetylene. When **105b** was subjected to the cyclization conditions it gave a mixture of vinyl silanes which, after cleavage of the silicon group, afforded β-agarofuran **102** in 66%. It was then discovered that the stereoselective reduction of **102** could be achieved using diimide. This reaction gave dihydroagarofuran **101a** from **102** in 92%. The material contained <5% of the epimer, **101b**.

In the last few years a number of workers have used radical cyclization in the course of organic synthesis. Both Hart[62] and Beckwith[63] have developed methods for the synthesis of functionalised perhydroindans.

Hart reduced m-methyl benzoic acid under Birch conditions and alkylated the anion with 4-bromo-1-butene to yield **106**. Iodolactonization (to **107**) and treatment with tributylstannane (AIBN initiated) in refluxing benzene yielded **109** as the major product in 47% yield. The minor product was the reduced material **108**.

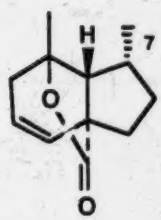


106



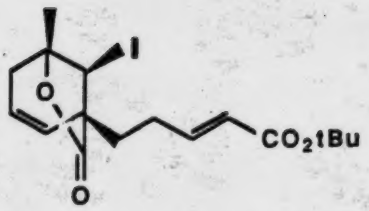
107 X = I

108 X = H

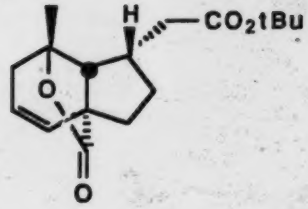


109

The stereochemistry of the major product **109** could be rationalized on the basis of the known preference of oxabicylco[3.3.0]octanes for cis-ring-fusion. The C-7 stereochemistry was consistent with the findings of Beckwith[37a] and Wolff[37b] with simpler systems. With the iodo ester **110**, the perhydroindan **111** was isolated in a synthetically useful yield of 73% and as a single isomer. This is the result of the enhanced reactivity shown in cyclizations occurring at the terminus of an enone. The stereochemistry of **111** was proved by conversion to **112** by treatment with lithium hexamethyldisilazide followed by trifluoracetic acid (82%).



110



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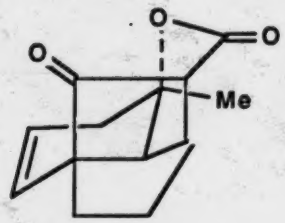
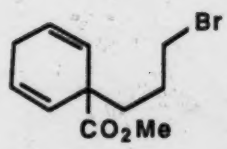


112

Beckwith was able to alkylate the anions derived from a number of aromatic substrates under Birch conditions. For example, the anion of methyl benzoate was alkylated with 1,3-dibromopropane to yield **113**. Cyclization of **113** with tributylstannane (AIBN initiated) in refluxing benzene yielded the perhydroindan **114** in 88%.[63]



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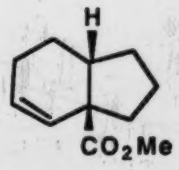
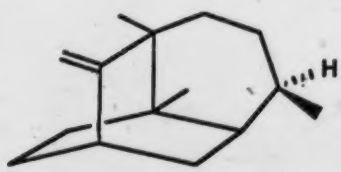


114

In the early nineteen eighties, Stork[64a] introduced the use of the vinyl radical in cyclization. This technique allows the synthesis of molecules containing a double bond (a site for further synthetic elaboration) in a predictable manner. The vinyl radicals can be easily generated by treatment of the appropriate vinyl halide with tributylstannane. Early experiments demonstrated the similarity of the reactive vinyl radicals with their well-investigated alkyl counterparts. A concern was the possibility of increased hydrogen abstraction from the hydride due to their relative instability with respect to alkyl radicals (ca. 10 kcal/mol less stable than ethyl radicals). This, however, was not found to be a problem, as in the cases examined cyclization appeared uninhibited. An example of the utility of vinyl radical cyclization can be found in the synthesis of seychellene **115**.[65] It should be noted that the stereochemistry of the vinyl halide **117** (Z or E) is not important since vinyl radicals undergo facile inversion prior to cyclization. Bicyclo[2.2.2]octane **116**, derived from 2,3-dimethyl cyclohexanone in 3 steps (25%), could be alkylated regioselectively with (E)-1,3-dibromo-2-butene to yield **117** in 80% yield.



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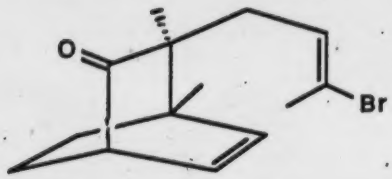
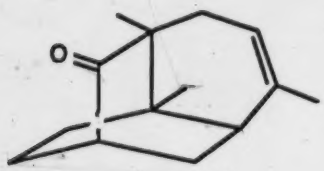


117

Treatment of **117** with tributylstannane (AIBN—initiated) in refluxing benzene yielded norseychellene **118** in 70% yield. Hydrogenation of **118** with 10% palladium on carbon in diethyl ether yielded norseychellanone **119** as the major product. This was converted into seychellene.



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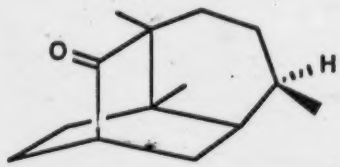
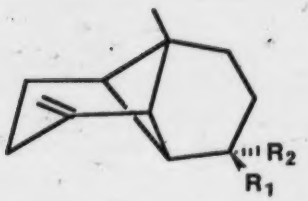


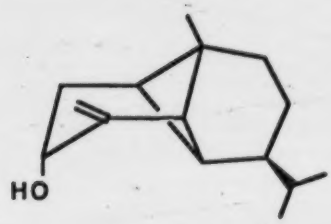
119

Snider[66] undertook the synthesis of β-copaene **120a**, its epimer β-ylangene **120b**, and the antitumor agent, lemalol **121**. Reduction of the bicyclic ketone **122** with lithium aluminum hydride and esterification with thiocarbonyldiimidazole yielded the imidazolide **123a**.



120a R_1 = H, R_2 = Me_2CH

b R_1 = Me_2CH, R_2 = H



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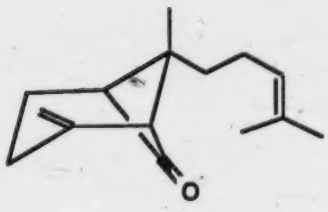

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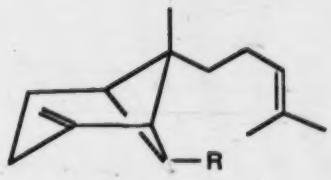


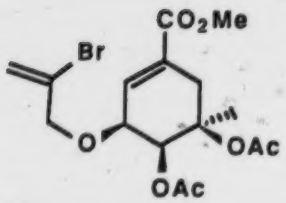
123 a R = OCSIm, b R = OH

c R = OCH_2SH, d R = H.

Im = Imidazole

Reaction of **123a** with tributylstannane (AIBN initiated) yielded **123b** (25%), **120a** (8%), **120b** (8%) and **123c** (40%). No reduction to β-trans-bergamotene **123d** was observed. Snider suggests that **123c** and **b** arise from partial reduction of the imidazolide due to the relative instability of the cyclobutyl radical that would be formed upon complete reduction of the imidazolide. Lemalol **121** was synthesized by treatment of **120b** with tert-butyl peroxide and selenium dioxide in 76% yield.

Hanessian[67] has employed radical cyclization for the synthesis of the hexahydrobenzofuran portion of the avermectins and milbemycins, potent anthelmintic agents. The precursor for cyclization, **124**, was derived from **126** in 8 steps.



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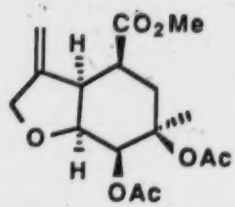

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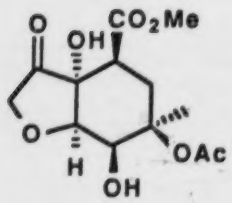

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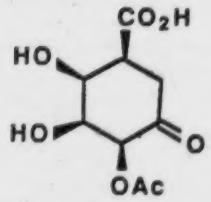
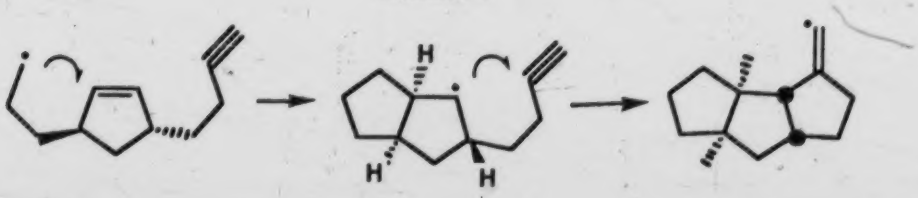


126

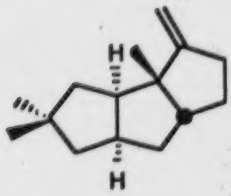
Treatment of **124** with triphenylstannane (AIBN—initiated) gave **125**. Ozonolysis, followed by treatment with lead tetraacetate, then produced the desired α-acetoxy oxahydrindane **127** in good yield. This represents the first synthesis of an oxahydrindane with the full compliment of functionality necessary for the total synthesis of avermectin B_{1a} and some of the milbemycins.

Curran has developed a strategy for the synthesis of condensed cyclopentanoids which allows two intramolecular cyclizations to occur *in tandem.* (Scheme 4).

Scheme 4



He has demonstrated this technique in the synthesis of (±)-hirsutene (the parent member of the hirsutane family of linear triquinanes) **128**,[68] Δ 9,12-capnellene **129**,[69] and (±)-silphiperfol-6-ene **130a** and its C-9 epimer **130b**.[70]



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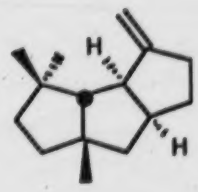

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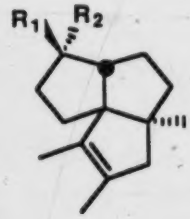
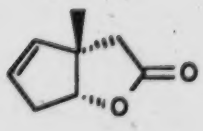


130 a R_1 = Me, R_2 = H

b R_1 = H, R_2 = Me

Hirsutene, **128**, was synthesized using the lactone **131**, derived from the cyclopentenylacetic acid via selenolactonization followed by selenoxide elimination. Treatment with the organo copper reagent derived from the bromide **132** yielded **133**, after removal of the tetrahydropyranyl protecting group.



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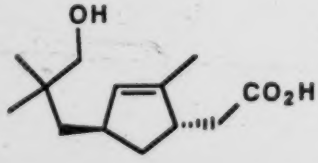
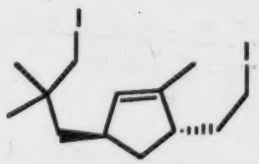
132

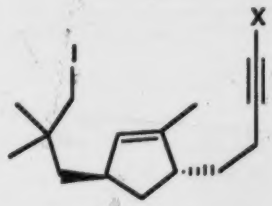


133

Reduction of the acid **133** with diisobutylaluminum hydride and treatment with trifluoroacetic anhydride gave the ditriflate, which afforded the diiodide **134** on exposure to tetrabutylammonium iodide.



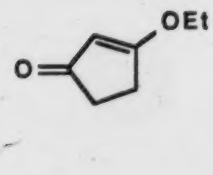
134



135a R = Me_3Si, **b** R = H

Preferential displacement of the primary iodide (versus the neopentyl iodide) with the lithium salt of trimethylsilyl acetylene gave **135a**, and removal of the trimethylsilyl group with cesium fluoride, gave **135b**. Treatment of the iodo acetylene with tributylstannane in refluxing benzene gave hirsutene **128** in 53% yield (from **135b**). A similar strategy was employed for the synthesis of $\Delta^{9,12}$-capnellene, **129**.

The precursor to cyclization for the synthesis of silphiperfol-6-ene was synthesized in ca. 45% yield by sequential alkylation of 3-ethoxy-2-cyclopenten-1-one **136** with methyl iodide and then with (E)-2-methyl-1,3-dibromo-2-butene to afford **137**. Reaction with the Grignard reagent derived from 4-bromo-1-butene yielded **138**.



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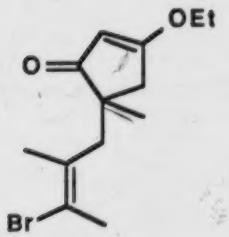
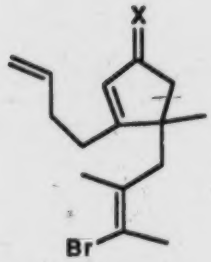


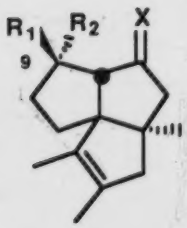
137



138 X = O

140 X = OCH_2CH_2O

Direct cyclization of **138** led to formation of the desired silphiperfollinone **139a** and its C-9 epimer **139b** in a ratio of 1:3.



139a R_1 = Me, R_2 = H, X = O

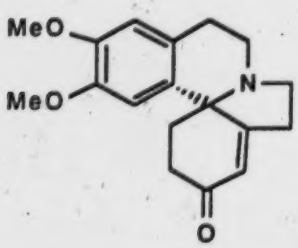
b R_1 = H, R_2 = Me, X = O

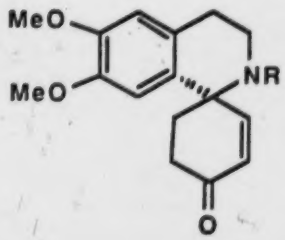
141a R_1 = Me, R_2 = H, X = $O(CH_2)_2O$

b R_1 = H, R_2 = Me, X = $O(CH_2)_2O$

Ketalization of **138** with ethylene glycol gave **140**. It was hoped that this would disfavor formation of the endo isomer (**139b**). Cyclization of **140** was effected in 65% yield and the two isomeric ketals (**141a** and **141b**) were separated and hydrolyzed individually to yield **139a** and **139b** in a ratio of 2.5:1. Wolff-Kishner reduction completed the synthesis of silphiperfol-6-ene, **130a** and 9-episilphiperfol-6-ene, **130b**.

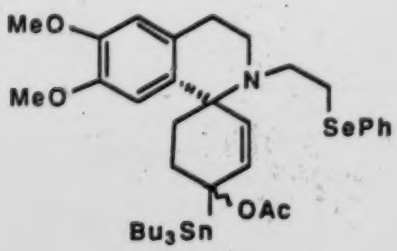
Danishefsky[71] has recently reported the total synthesis of (±)-3-demethoxyerythratidinone **142** employing a novel type of intramolecular cyclization.

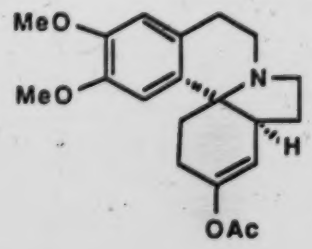




142 **143** R = H, **144** R = $(CH_2)_2SePh$

Spiro quinoline **143** was synthesized in a number of steps from cyclohexa-1,4-dione and dopamine dimethyl ether. The reductive amination of **143** with (phenylseleno)acetaldehyde (using sodium cyanoborohydride) yielded **144**. Treatment of this ketone with lithio tributylstannane, followed by immediate acylation (acetic anhydride), gave **145** as a 1:1 mixture of epimers. Cyclization of **145** mediated by tributylstannane gave **146** as a single isomer. This enol acetate was then modified via its derived α-phenylseleno ketone to **142**.

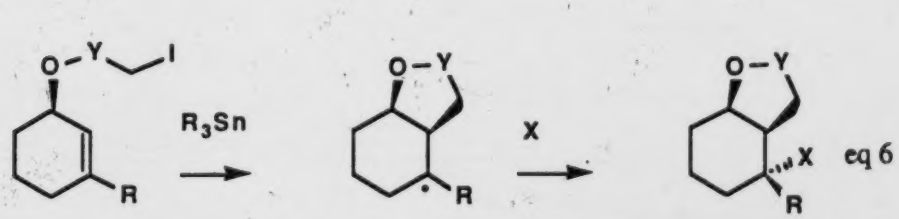




145 **146**

Radical cyclization can also be used in a manner that leads to predictable stereochemical results.

Stork,[72] for example, has contributed to this area. He exploited the fact that the cyclization depicted below (equation 6) results in a product with a cis-ring-fusion. The resulting radical **147** can now abstract hydrogen from either the solvent or a trialkyl stannane or it can react with a suitable radical trap to give, by virtue of the concave shape of radical **147**, the product **148**, with predictable stereochemistry.



eq 6

147 **148**

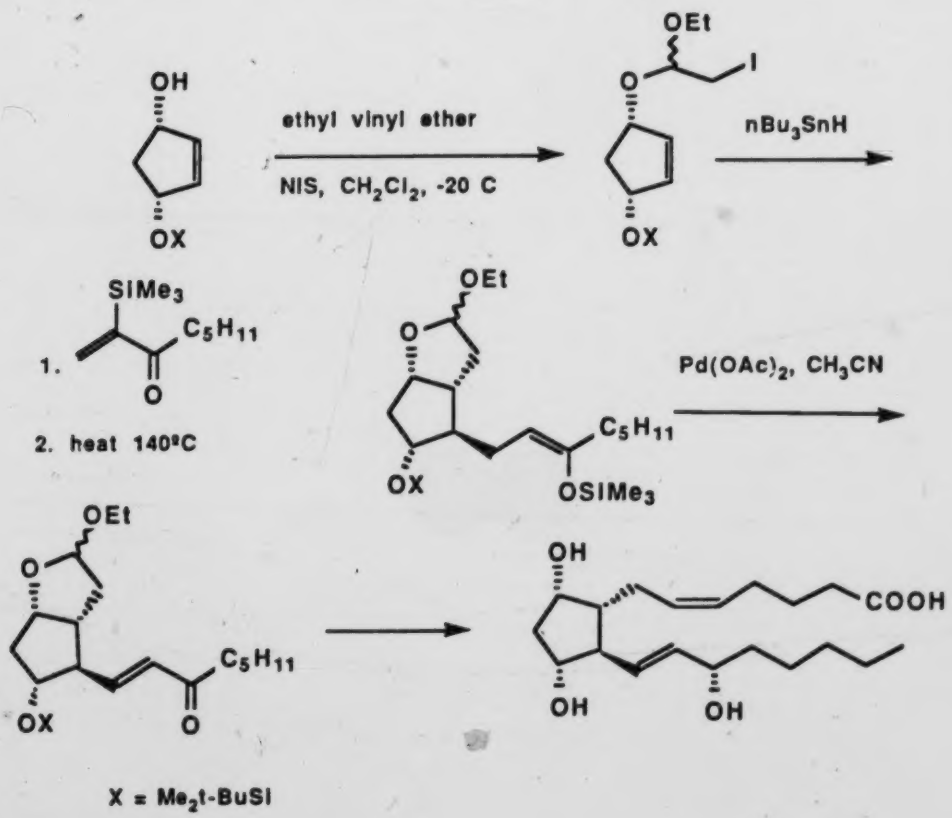
X = for example H, tert-BuNC, phenyl vinyl sulphone, methyl acrylate

Y = CH(OEt), CMe(OMe) or $SiMe_2$

To reduce the amount of reduction of radical **147**, the reaction can be done under photolytic conditions using hexaphenylstannane as a source of the necessary trialkyl stannyl radical. This procedure has a number of drawbacks including the necessity to remove an insoluble and opaque film of a polymeric tin species from the walls of the reaction vessel during the course of the experiment. Stork later developed

conditions which allow the efficient trapping of radical **147** in the presence of a trialkyl stannane. The substrate and an excess of the radical trap are dissolved in degassed tert-butyl alcohol along with sodium cyanoborohydride, tributyltin chloride (0.1 equiv.) and AIBN (0.1 equiv.). The reaction mixture is then refluxed for a number of hours. A demonstration of the utility of this method is portrayed in Scheme 5 for the synthesis of (+) prostaglandin $F_{2\alpha}$ **149**.[73]

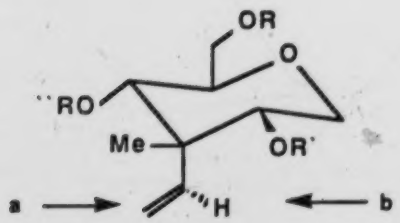
Scheme 5



149

Stork[74] has also developed a similar method for the α-hydroxymethylation of allylic alcohols.

Methods starting with sugars and other readily available optically pure natural products for the synthesis of enatiomerically pure molecules have recently become powerful tools for the synthetic organic chemist. Fraser-Reid[75] has employed radical cyclization for the synthesis of optically pure annulated sugars. Such compounds have been shown to be important in the synthesis of optically pure carbocycles. He observed that molecules such as **150** undergo facial selective epoxidation which is controlled by whichever hydroxy group is left unprotected. The implication of this is that **150** is reacting with the pendant vinyl group orientated exclusively in the exo-position (as drawn). Models indicate that both rotamers of **150** should be reactive.

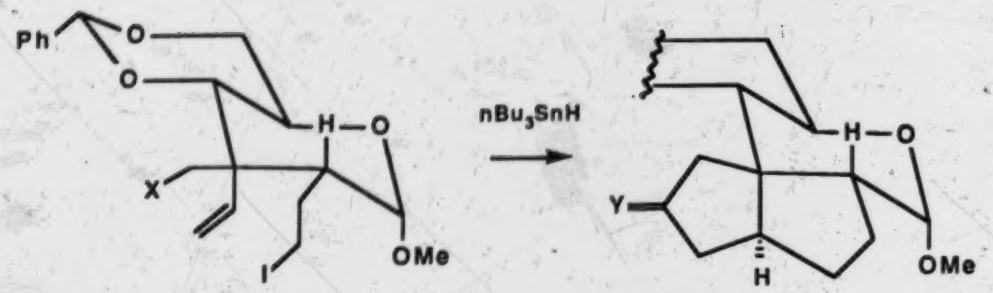


R' = H attack side **b**

R" = H attack side **a**

150

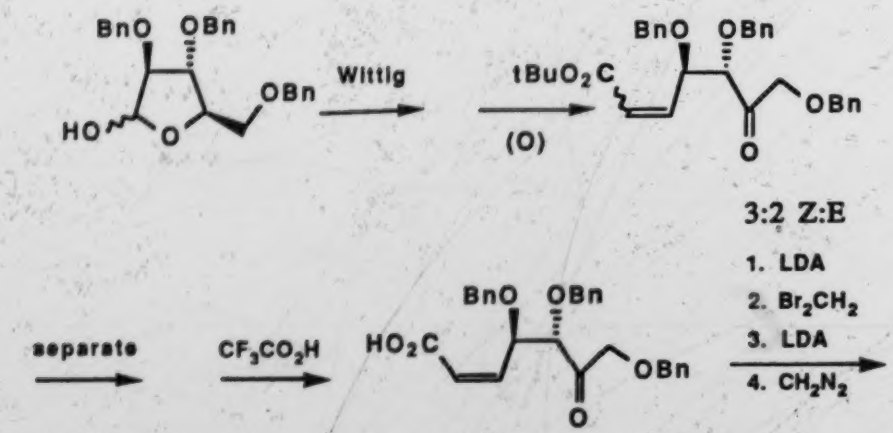
Thus, by fixing suitably disposed pendants on the sugar 'frame', the synthesis of annulated pentalenes **152** from **151** was achieved.

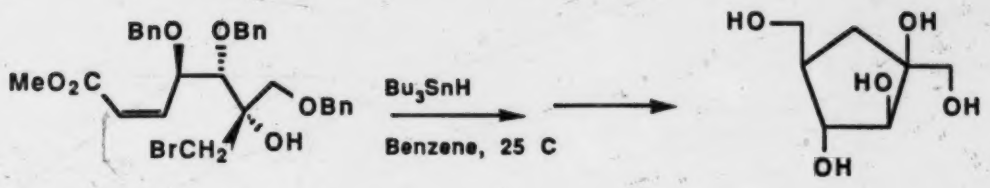


151 X = CN, C=C 152 Y = O, CH_2

Wilcox[76] has developed a method for the synthesis of optically active polyhydroxylated cyclopentanes. He has applied the method[76] to the synthesis of the carbocyclic analogue of D-fructofuranose, a potent inhibitor for phosphofructokinase and an inhibitor for 1,6-diphosphofructo-1-phosphatase (Scheme 6). The synthesis commences from an inexpensive arabinose derivative.

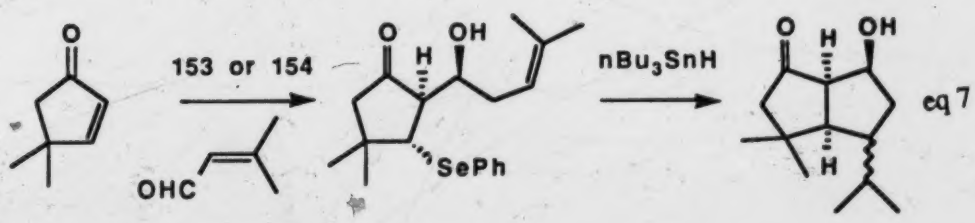
Scheme 6





carba-D-fructofuranose

Recently Livinghouse[78] has reported a method for stereoselective synthesis of fused pentalenones (equation 7). Treatment of a cyclic enone **155** with (phenylseleno)dimethylalane **153**, or lithium (phenylseleno)tetra(isopropoxy)titanate **154**, gives an intermediate which can undergo an aldol reaction with a suitable unsaturated aldehyde to produce the β-hydroxy ketone **156** with an erthyro:threo ratio of >20:1 in 72% yield. Slow addition of tributylstannane over 16 h gave **157** in excellent yield (95%) as a 1 : 1 mixture of epimers.



155 **156** **157**

153 = $PhSeAlMe_2$ **154** = $LiPhSeTi(iOPr)_4$

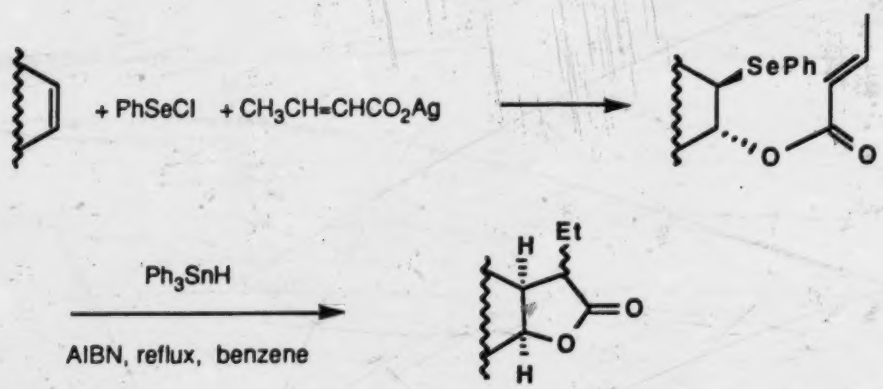
Work from Clive's laboratory has also contributed to the area of radical cyclization[79] and relevant parts of this research are mentioned in the next section.

II RESULTS AND DISCUSSION

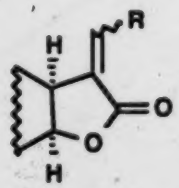
Part 1 Methods for the synthesis of γ-Lactones.

Earlier work in this laboratory was successful in developing a method for the synthesis of γ-lactones from alkenes (Scheme7).[80]

Scheme 7



We wished to see if this method could be applied also to the preparation of α-alkylidene γ-lactones **158** via the analogous acetylenic esters. α-Methylene lactones (**158**, R = H) are important structural units of ca. 10% of all natural products.[81]

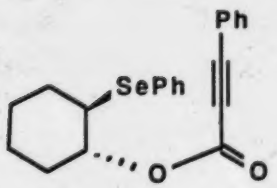


158

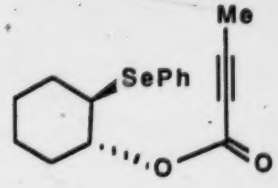
A number of esters were prepared (Table 3). The required acids were readily available. 2-Butynoic acid[82] and 3-phenyl-2-propynoic acid[83] were prepared by literature procedures.

Table 3 (X refers to X in PhSeX)

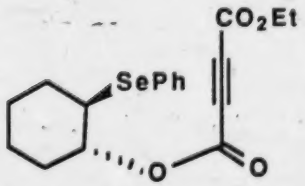
Preparation of β-Phenylseleno 2-propynoates.



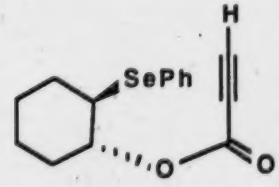
159 X = Br 75%, X = Cl 49%



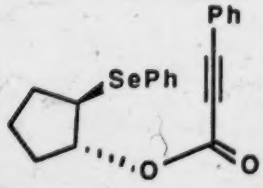
160 X = Br 67%, X = Cl 63%



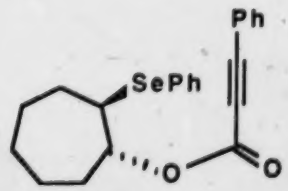
161 X = Br 27%



162 X = Cl 80%



163 X = Br 80%, X = Cl 47%



164 X = Br 67%

Ethyl 2-butyndioic acid (**165**) was made by deprotonation of ethyl 2-propynoate with n-butyllithium and reaction of the resultant lithium salt with carbon dioxide. Distillation of the residue gave the pure acid in 69% yield. We found that the cesium salts of the acetylenic acids were effective in the preparation of the esters (see

Table 3), and that the use of phenylselenenyl bromide generally gave better results than phenylselenenyl chloride.

The (phenylseleno)cycloalkyl esters were prepared by addition of the appropriate cycloalkene to a solution of the phenylselenenyl halide in acetonitrile until the solution was decolorized. Then the acid salt was added and the mixture was sonicated overnight at room temperature. Chromatography over silica gel gave the pure β-phenylseleno esters **159-164**. The assignment of trans stereochemistry was based upon literature precedent (for the addition of selenium species to olefins) and earlier work done in these laboratories.[80, 84]

Unfortunately, only the 3-phenyl-2-propynoates **159, 163** and **164** cyclized when treated with triphenylstannane.* In these cases give the γ-lactones **166, 167** and **168** were formed. Lactones **167** and **168** were inseparable (chromatography over silica gel) mixtures of cis- and trans-ring-fusion isomers. The other 2-propynoates gave only complex reaction mixtures and high molecular weight products, possibly arising from addition of the stannane to the triple bond. In the successful reactions, only cyclized materials were recovered and no reduced materials were detected (TLC).

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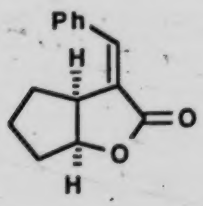
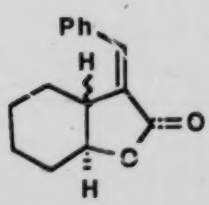
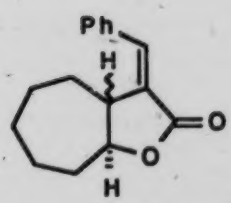
* The radical cyclizations reported in this thesis were carried out by the slow addition of a benzene solution of triphenylstannane and a benzene solution of initiator (AIBN) to a refluxing solution of the substrate, also in benzene. The two solutions were added simultaneously using a double syringe pump. After the addition was complete (ca. 8 h) the solution was refluxed for an arbitrary period (ca. 8h). The reactions were done overnight for convenience. It may be possible to dispense with the additional period of refluxing. The stannane and initiator can be mixed in one solution allowing a single syringe pump to be employed. Also periodic addition of the reagents, in portions, using an addition funnel or syringe may be effective.



166 74% 100:0*



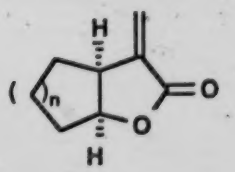
167 72% 95:5*



168 69% 50:50*

*ratio of cis:trans-ring-fusion.

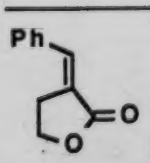
The IR absorption frequencies of the compounds **166-168** (1745-1760 cm^{-1}) were in agreement with the presence of a γ-lactone unit.* The OC-H proton chemical shifts for **166-168** are in accord with those for the analogous α-methylene lactones **169**.[86] The cis-ring-fusion stereochemistry for **167** and **168** was also confirmed by Nuclear Overhauser Difference spectroscopy. Each ring junction proton gave enhancements of ca. 10% upon irradiation of the other proton. In cis-ring-fused 2-oxabicyclo[4.3.0]nonan-3-ones the CH-O signal occurs at δ 4.3-4.65. In the analogous trans isomers, the corresponding signal occurs at δ 3.60-3.78.[87]



169

NMR DATA

	$CDCl_3$	$CDCl_3$
169	n = 1 δ 4.99	**166** δ 5.05
	n = 2 δ 4.53	**167** δ 4.50
	n = 3 δ 4.67	**168** δ 4.70



IR (C=O) 1742 cm^{-1} (see ref 85).

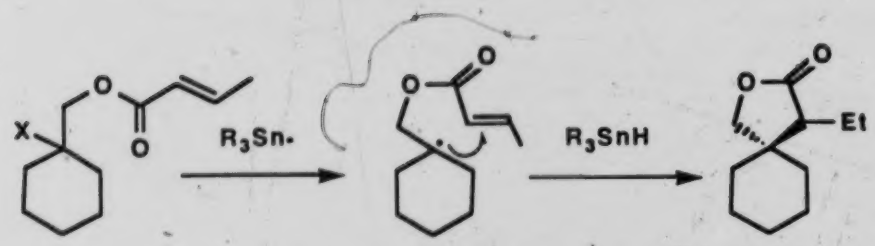
The resonance for the olefinic proton of **166-168** is obscured by the signals for the phenyl group between δ 7.3 and δ 7.4. This downfield shift suggests the (E) stereochemistry depicted where the olefinic proton is deshielded by the carbonyl group of the γ-lactone. A definite assignment of (E) stereochemistry for the double bond geometry would require a knowledge of the chemical shift for the vinyl proton of the (Z) isomer. The ^{13}C spectra were consistent with the presence of one isomer for the alkene stereochemistry in each of the compounds **166-168**.

There are examples in the literature where radical mediated intramolecular cyclizations yield sterically congested products.[88] Due the exothermicity of intramolecular radical addition the transition state resembles the reactant. This reduces the susceptibility of the process to steric effects.

The generation of quaternary centers by ionic processes has been intensively studied.[89] We hoped to develop a method using radical reactions for the synthesis of spirocyclic compounds. We initially investigated the synthesis of spirolactones (Scheme 8).

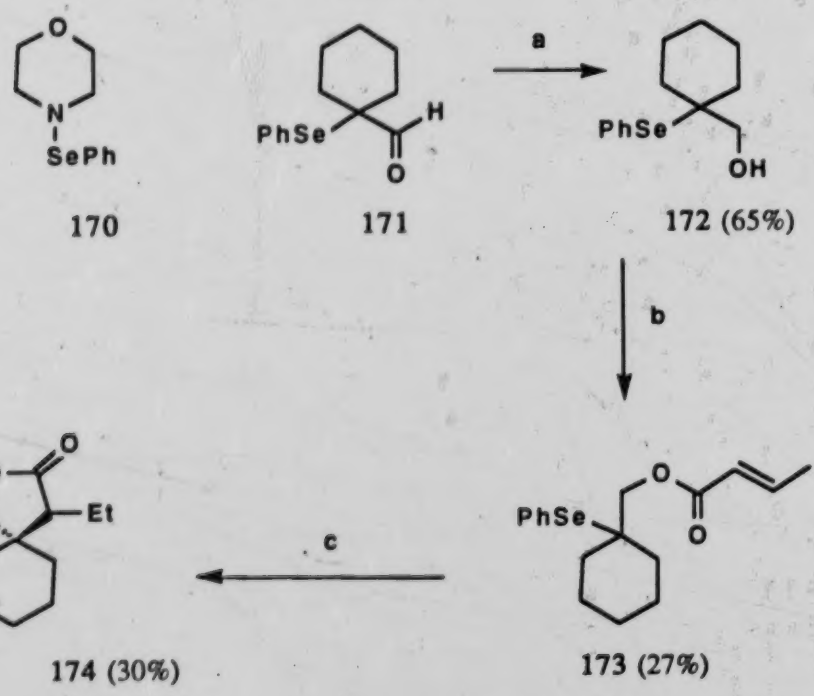
We were quickly able to show that the method worked—at least in principle. Compound **171**, 1-(phenylseleno)cyclohexanecarbaldehyde, was prepared in moderate yield (53%) by the reaction of N-(phenylseleno)morpholine **170**[90] (generated in situ from morpholine and phenylselenenyl bromide) with cyclohexanecarbaldehyde. Reduction of the aldehyde with sodium borohydride and esterification of the alcohol

Scheme 8



X = Cl, Br, NO_2, SePh.

Scheme 9



170 171 172 (65%)

173 (27%) 174 (30%)

a) $NaBH_4$ (1.5 equiv.), EtOH, -30°C to r.t., 3 h. b) trans-2-butenoyl chloride (1.05 equiv.), pyridine (1.05 equiv.), DMAP (10 mol%), CH_3CN, 3 h, r.t. c) Ph_3SnH (1.25 equiv.), AIBN (14 mol%), slow addition 8 h, reflux benzene 18 h.

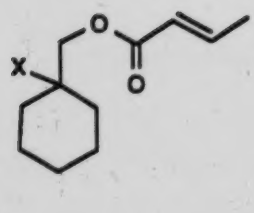
DMAP = 4-N,N-dimethylaminopyridine.

with trans-2-butenoyl chloride gave the required ester **173** (Scheme 9). Slow addition of benzene solutions of triphenylstannane and AIBN to a refluxing benzene solution of the ester yielded the 2-oxaspiro[5.4]decan-3-one **174** (30%).

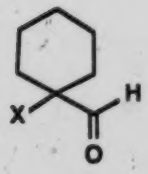
It was clear that a better route to the ester **173** was needed and that the yield of the cyclization had to be increased.

We attempted to investigate the use of **175a**, **b**, and **c**, as precursors for cyclization. Compound **175c** was prepared directly from nitrocyclohexane and we felt that **175a** and **175b** should be accessible from the appropriate α-halo aldehydes. Aldehyde **176a** was made according to a literature[91] procedure by slow addition of bromine to a chloroform solution of cyclohexanecarbaldehyde in the presence of calcium carbonate.

Several attempts to prepare the alcohol **177a** derived by the sodium borohydride reduction of **176a** were unsuccessful, leading to the formation of polymeric material. Also, attempts to isolate the product when **176a** was reduced and esterified without purification met with failure despite the fact that the ^{1}H NMR spectrum of the crude material indicated the presence of the desired ester.



175



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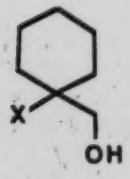
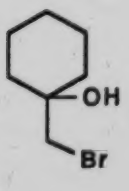


177

a X = Br, **b** X = Cl **c**, X = NO_2

Our failure was surprising because of the reported preparation of the bromoalcohol **177a** by an alternative route.[92] A closer inspection of the literature revealed a report by Sisti,[93] who prepared the isomer **178** and determined that it was identical to the compound claimed as having the structure **177a**.



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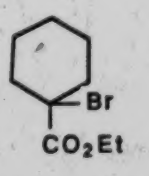


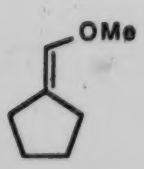
179

Sisti attempted to prepare the bromo alcohol **177a** by reduction of the α-bromo ester **179**. He failed to obtain the pure alcohol but instead found that successive attempts at isolation of the product resulted in an increase in the amount of decomposition. He concluded that the tertiary bromide was extremely labile.

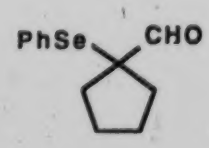
The synthesis of the chloroester **175b** was successful. Reduction of the aldehyde **176b**[94] with sodium borohydride, and immediate esterification with trans-2-butenoic anhydride under basic conditions, gave ester **175b** in 53% yield. Similarly, 1-nitro-1-cyclohexanemethanol[95] **177c** was acylated to give ester **175c** in 76% yield. The required alcohol, **177c** was prepared by hydroxymethylation of nitrocyclohexane with paraformaldehyde under basic conditions.

Chloroester **175b** was cyclized using triphenylstannane to the spirolactone **174** in 53% yield. Attempts to do likewise with the nitro ester **175c** were not as successful. The reaction failed to go to completion and resulted in only partial denitration and cyclization. Radical chain reactions are quite sensitive to impurities, but the use of carefully purified ester did not result in any improvement in the radical cyclization.

We also investigated alternative routes to the α-phenylseleno aldehydes (such as **171**). One method involved reaction of the methyl vinyl ether **180** with phenylselenenyl chloride. This gave **181** after hydrolysis.



180



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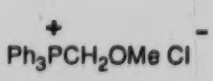
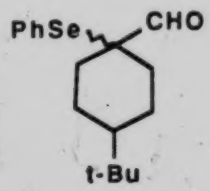


182

This reaction went only in a modest (52%) yield. We also encountered problems in preparing the required methyl vinyl ether via a Wittig reaction using the ylide derived from **182** by the action of potassium tert-butoxide,[96] but we did not attempt to optimize this reaction in view of the selenation result.

Krief[97] reported the preparation of aldehyde **183** by reaction of selenoacetal **184** with n-butyllithium to form the α-phenylseleno anion **186**. Reaction of this anion with dimethylformamide gave the aldehyde **183** in 46% yield. We repeated this reaction and obtained **183** in 66% yield. This reaction was later optimized and the yield was raised to ca. 80%. Due to the availability of selenoacetals[98] from the corresponding ketones we decided to adopt this approach.



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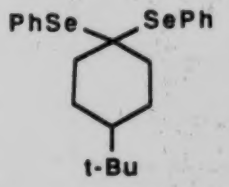

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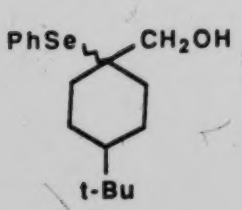

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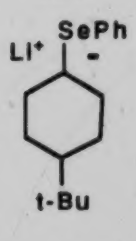
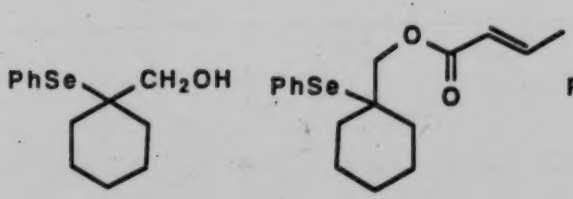


186

Reduction of the aldehyde **171** with sodium borohydride gave the alcohol **172** in 65-80% yields. The use of sodium borohydride did not appear to be general for it did not work well with aldehyde **183**.

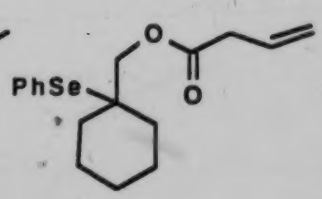
Sodium borohydride, lithium aluminum borohydride and lithium tri(tert-butyloxy) aluminum hydride were ineffective for the reduction of **183**, yielding largely diphenyl diselenide, presumably via carbon selenium bond cleavage in the aldehyde. Lithium borohydride and sodium cyanoborohydride gave the alcohol **185** in 53% and 30% yield, respectively. It appeared that nucleophillic hydride reducing agents were not suitable and we turned our attention to electrophillic reducing reagents such as borane as a complex with dimethyl sulfide. Stirring **183** with borane-dimethyl sulfide complex in dichloromethane for 3 h at room temperature gave **185** in 75% isolated yield. This reduction turned out to be generally applicable to the substrates that we subsequently investigated.

Acylation of the α-phenylseleno alcohols also proved to be troublesome. Reaction of alcohol **172** with trans-2-butenoyl chloride and trans-2-butenoic anhydride under a variety of mildly basic conditions gave the ester **173** in yields of only 40-60%. However, when alcohol **185** was reacted with acetic anhydride in pyridine, the acetate was isolated in 81% yield.



172

173



187

It was also interesting to observe that, when the alcohol **172** was allowed to react with trans-2-butenoyl chloride with triethyl amine as base, the β,γ-unsaturated ester **187** was isolated instead of the expected **173**. This rearrangement has been previously, investigated by Ozeki.[99] He suggested that the β,γ-unsaturated ester arises by formation in situ of vinyl ketene which then acylates the alcohol to give **187**. In our hands, this reaction was reproducible and it gave **187** in 75% yield.

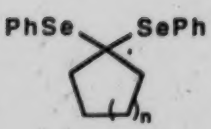
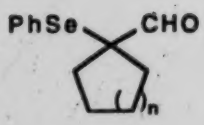
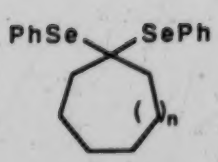
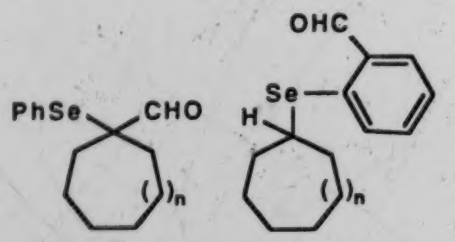
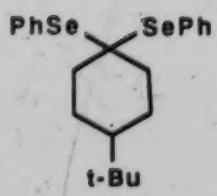
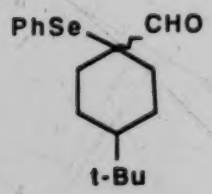
Attempts to acylate the sodium alkoxide (prepared with sodium hydride) were also unsuccessful. Deprotonation of **172** at -78°C with n-butyllithium in THF and addition of an excess of trans-2-butenoyl chloride yielded the ester **173** in 75-80% yields. We ran the reaction several times and the yields indicated are the best we could obtain.

We had now established a reasonably efficient synthetic route to the phenylseleno esters required for cyclization to spirolactones. This route involved preparation of the α-phenylseleno aldehydes from selenoacetals, reduction to the corresponding alcohols with borane-dimethyl sulfide complex, and esterification employing the lithium alkoxide and trans-2-butenoyl chloride. A number of examples (Tables 4,5 and 6) were investigated.

Treatment of the selenoacetals with n-butyllithium in THF at -78°C and quenching of the α-phenylseleno anion with dimethylformamide gave the α-phenylseleno aldehydes in good yields (Table 4). Selenoacetals **190** and **193** gave

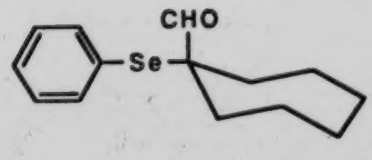
Table 4

Preparation of Selenoacetals and α-Phenylseleno aldehydes.

acetal (method)[a]	α-phenylseleno aldehydes
	
188 n=1 (A) 54%	181 n=1 84%
189 n=2 (B) 62%	171 n=2 90%
	
190 n=1 (B) 48%	191 n=1 192 n=1 74%[b]
193 n=2 (B) 38%	194 n=2 195 n=2 52%[c]
	
184 (B) 62%	183[d] 81%

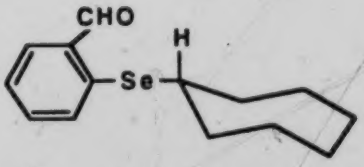
[a] (A) PhSeH (2 equiv.), $ZnCl_2$ (0.5 equiv.), CCl_4; (B) PhSeH (2 equiv.), conc H_2SO_4 (1.5 equiv.), CCl_4. [b] As a mixture 51:49. [c] Ratio undetermined; converted directly to alcohols. [d] One isomer, stereochemistry not assigned.

mixtures of formyl compounds. This was initially ascertained for **190** by the appearance of two aldehyde signals in the ^1H NMR spectrum of, what appeared (TLC) to be, a homogeneous product. Purification using centrifugal chromatography gave the two individual aldehydes and their structures were easily assigned.



191 ν (C=O) = 1707 cm^{-1}

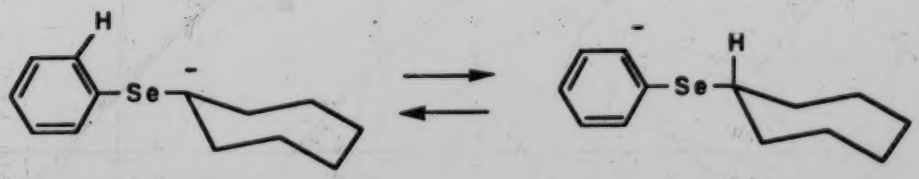
δ (CHO) = 9.2



192 ν (C=O) = 1693 cm^{-1}

δ (CHO) = 10.4

The two products presumably arise from electron transfer (via a proton shift) of the initially formed anion **196** to **197**



196 **197**

Although we have no firm evidence for the ortho disposition of the formyl group in **192**, the literature suggests that electron transfer occurs to the o-position of the aromatic ring to yield the more thermodynamically stable aryl lithium.[100] We found that, in order to reduce the amount of **192** and **195** (see Table 4), it was advisable to

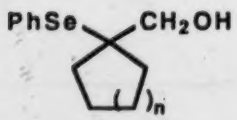
quench the anion (such as **196**) ca. 5 min after the addition of the n-butyllithium was completed.

The aldehydes **181**, **171** and **191**, **194**, **183** were then reduced with borane-dimethyl sulfide complex in dichloromethane at room temperature. The results are shown in Table 5.

The alcohols **198**, **172**, **200**, and **203** were esterified by deprotonation with n-butyllithium in THF and quenching the lithium alkoxide thus produced with trans-2-butenoyl chloride (2-3 equiv.). However, alcohol **185**, when reacted under similar conditions, gave ester **206** in only 30% yield. This problem was overcome by treating the alcohol with potassium tert-butoxide (1.1 equiv.) in a 3:2 mixture of THF and diethyl ether at -30°C, followed by addition of trans-2-butenoyl chloride. This procedure gave **206** as a single isomer in 71% yield.

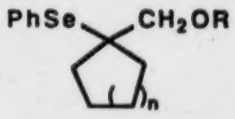
Table 5[a]

Preparation of β-Hydroxyselenides and β-Phenylseleno esters.



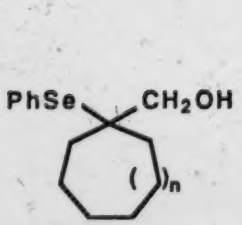
198 n = 1 88%

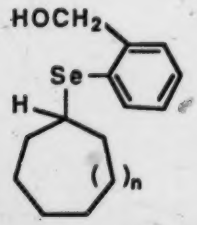
172 n = 2 76%



199 n = 1 74%

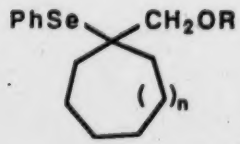
173 n = 2 75%





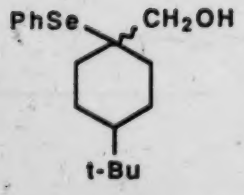
200 n = 1 30% 201 n = 1 33% [b]

203 and 204 n = 2 53% [c]

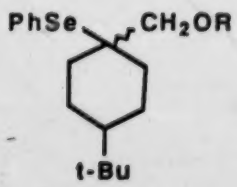


202 n = 1 65%

205 n = 2 72%



185 77%



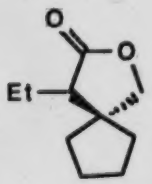
206 71% [d]

[a] R = $COCH{=}CHCH_3$. [b] From mixture of formyl compounds 191 and 192. [c] From mixture of formyl compound 194 and 195. [d] See discussion; one isomer, stereochemistry not assigned.

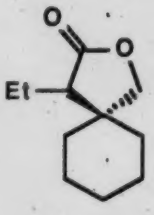
Cyclizations were effected by the slow addition of two solutions [i) AIBN (10-15 mol%) in benzene and ii) triphenylstannane (1.3-1.5 equiv.) in benzene] to a refluxing solution of the individual esters. The results are collected in (Table 6).

Table 6

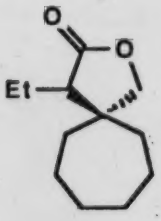
Cyclization of β-phenlyseleno esters to spiro-γ-lactones.



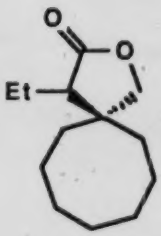
207 73%



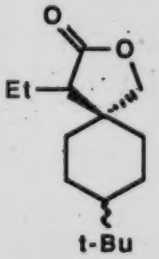
174 70%



208 67%

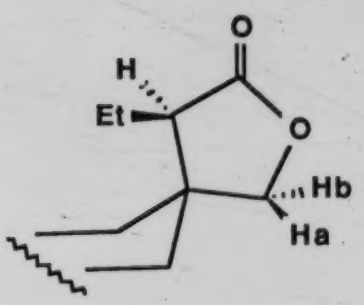


209 60%



210 86%

In no case, was any of the reduced ester detected (TLC). The products could be separated easily from the organotin residues by flash chromatography. The spirolactones had characteristic infrared carbonyl absorption frequencies at 1775 cm^{-1} for the γ-lactone unit. Also the ^1H NMR spectra displayed a prominent AB absorption pattern for the lactone methylene protons (H_a and H_b) in which J_{AB} was 8-10 Hz.



Cyclization of the tert-butylcyclohexyl ester **206** yielded an inseparable mixture of lactones **210**, isomeric at the spiro carbon in a 60:40 ratio. The ^{13}C NMR spectra of the aldehyde **183**, alcohol **185** and ester **206** indicated that only one isomer was present, i.e. the phenylseleno group exists in only one orientation. To confirm this, we studied the ^{77}Se NMR spectrum of the ester **206**. The isotope ^{77}Se has favorable NMR properties: I = 1/2, natural abundance = 7.6% and thus the receptivity of the isotope is 2.98 times that of the ^{13}C isotope. Duddeck[101] has published a report on the dynamic ^{77}Se properties of phenylseleno substituted cyclohexane derivatives. The ^{77}Se nucleus is subject to an extremely large γ-diamagnetic effect of 30-40 ppm/ γ-gauche CH_2. Thus axial and equatorial phenylseleno groups in cyclohexane exhibit large differences in ^{77}Se chemical shifts (70-80 ppm). Ester **206** shows only one signal at 510 ppm * (signal to noise ratio 20:1) at 294°K. It is not possible to assign an axial or equatorial conformation on the basis of this evidence. The formation of two isomers in the cyclization is attributable to approach of the pendant side chain to both lobes of the radical SOMO (due a the planer geometry of radicals). As expected unless

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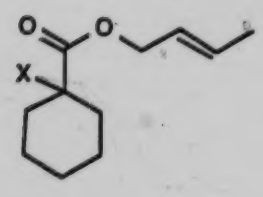
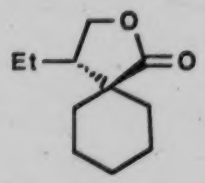
* Recorded at 38.17 MHz, chemical shift relative to diphenyl diselenide at δ 462.6 in $CDCl_3$ at 293°K. ^{77}Se shifts are temperature dependent.

steric constraints determine otherwise there is no significant retention of stereochemistry in the reaction.

We also investigated the cyclization of ester **211**



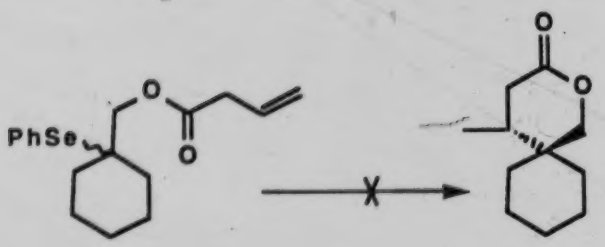
211 X = SePh, **213** X = H



212

Ester **211** was prepared by reaction of selenoacetal **189** with n-butyllithium followed by quenching with trans-2-butenyl chloroformate.[102] Cyclization under the standard conditions outlined above gave a mixture of the spirolactone **212** (34%) and the reduced ester **213** (16%). It was interesting to note the isolation of the reduced product in this case. It is known that α-ester groups tend to stabilize an adjacent radical.[103] Since part of this stabilization is presumably derived from delocalization (isoelectronic with allyl radical), this would lead to an increased barrier for rotation around the C-C=O bond. For cyclization to occur, Drieding models indicate that the carbonyl π-system must be almost orthogonal to the radical SOMO. These effects perhaps lead to an increased $\Delta H^{\ddagger}$ for the cyclization and allow the reduction to compete more effectively.

Attempts to effect the 6-exo cyclization using ester **187** were also unsuccessful (eq. 8).

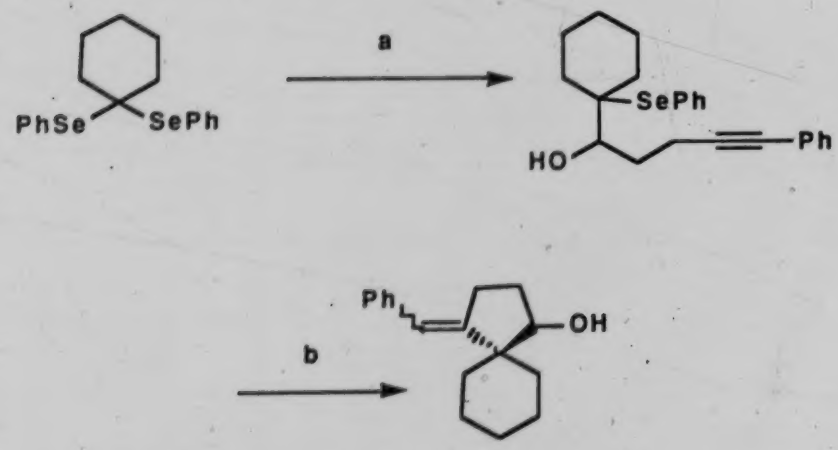


eq 8.

187

During the course of this work, Lu Set[104] (of our laboratories) developed a route to carbocyclic spiro compounds (Scheme 10).

Scheme 10



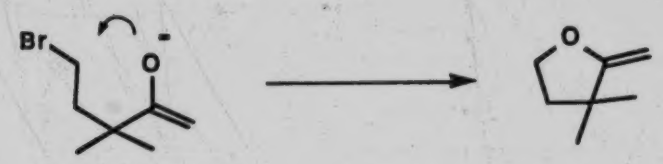
a) n-BuLi (1 equiv.), THF -78°C 5 min, 5-phenylpent-4-ynal

b) Ph_3SnH, AIBN reflux benzene.

Therefore, by employing the selenoacetals as a common starting point, the synthesis of spirolactones and spirocarbocycles can be achieved. These cyclizations occur in the presence of an ester or an alcohol (Lu Set) without the need for protection.

Part 2 The Synthesis of Carbocycles.

In the mid seventies, Baldwin[32] suggested a set of empirical rules for ring closure reactions which enable the synthetic chemist to predict the feasibility of a ring forming reaction (see p. 10). As part of his research Baldwin studied the intramolecular alkylation reactions of ketone enolates. He found that, due to the appreciable double bond character of a ketone enolate,[105] there was a strong kinetic barrier against 5-(enolendo)-exo-tet[106] and 5-(enolendo)-exo-trig[107] closures.* For example, the enolates **214** and **215**, formed from reaction of the corresponding bromo ketones with lithium diisopropylamide or potassium tert-butoxide, afford completely different classes of compounds.[106]

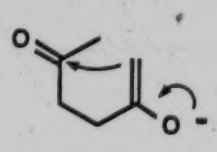


214

215

*Enolendo means that the enolic double bond is endocyclic in the ring being formed. Exo-tet and exo-trig refer to the intramolecular attack of the enolate on a tetrahedral carbon (sp^3) or a trigonal carbon (sp^2) exocyclic to the ring being formed.

Carbocyclic ring closure of the ambident enolate nucleophile **214** is equivalent to the disfavored 5-endo-tet process. In compound **215** the corresponding reaction is equivalent to the favored 6-endo-tet closure.[32] For **214**, the alternative reaction course is O-alkylation, as shown. The electrophillic carbon (CH_2Br) can approach orthogonally to the enolate π-system (O-alkylation) but not in the plane of the enolate π-system (C-alkylation). In **215** the increased carbon chain length allows C-alkylation to occur. The case of intramolecular aldol condensations is similar. The closure shown in **216** is kinetically disfavored.



216 5-(enolendo)-exo-trig

This closure is not observed when an alternative intramolecular pathway is available which does not involve the barrier implicit in **216**.[107]

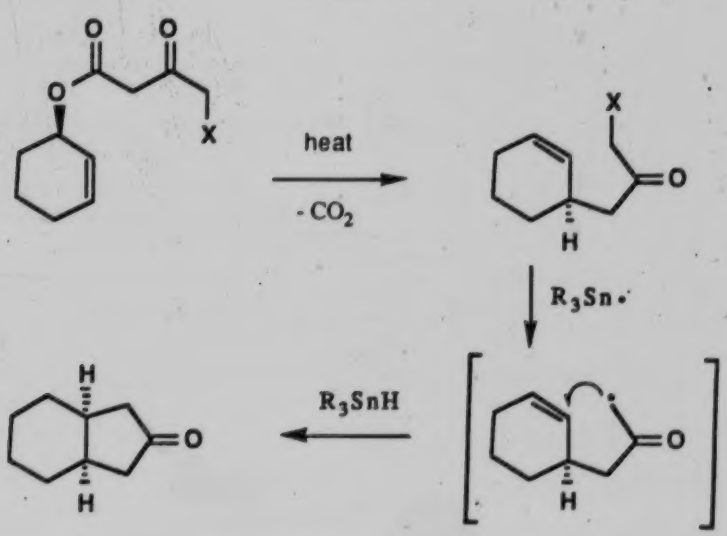
The C1-C2 bond of α-keto radicals [108,109] such as **217** is essentially a single bond; **217** is the major resonance hybrid (ca. 85%). This results in a lower C1-C2 rotational barrier (9 kcal/mol[108] for **217** versus > 27 kcal/mol[105] for **216**). The steric factors favouring O-alkylation over C-alkylation for **214** should be absent or greatly reduced in **217**.

217 218

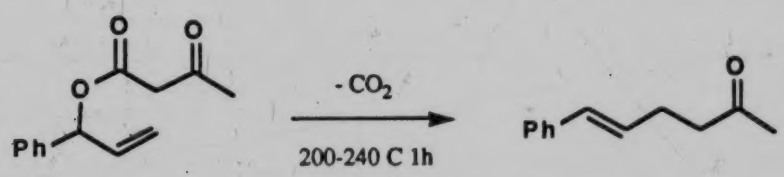
We wished to see if the radical **217** would cyclize to the cyclopentanone **218**, a process analogous in its result to the disfavored 5-(enolendo)-exo closure of **216**.

We chose the Carroll reaction as a possible route to the ketones required for our study (Scheme 11).

Scheme 11



This rearrangement was discovered by Carroll in 1940,[110] and more thoroughly investigated by Cope[111] in 1943. The rearrangement involves thermolysis of allylic esters of 3-oxobutanoic acid to give unsaturated methyl ketones, as shown in equation 9.



eq 9

219 **220**

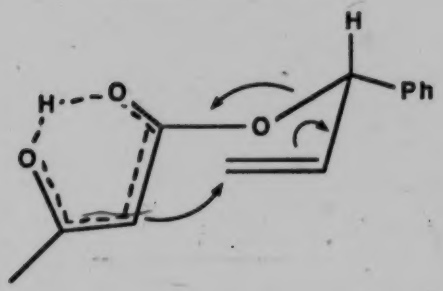
The 3-oxobutanoates can be prepared by reaction of the appropriate alcohol with diketene. The reaction is catalyzed by a small amount of the sodium alkoxide of the alcohol (equation 10).

eq 10.

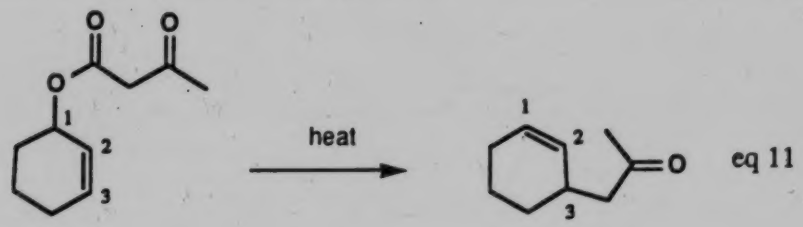
Hill[112] noted that the reaction shows some stereoselectivity and, like Cope, he observed the formation of trans-unsaturated ketone **220** from the 3-oxobutanoate **219**. The reaction resembles the Claisen rearrangement. Hill suggested that the transition state for the process leading to the stereospecific formation of the trans-ketone was chair-like (Figure 2).

Figure 2

Carroll rearrangement.



The only example that we could find of the Carroll rearrangement performed on a cyclic substrate was that done by Hill (equation 11).

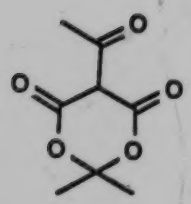


eq 11

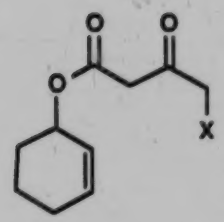
He found that the rearrangement was similar to the Claisen rearrangement in that there was a retention of stereochemistry at the reacting carbon center, C-3 (see equation 11).

We prepared the β-ketoester **222** in moderate yield using a method described by Yonemitsu.[113] Reaction of acetyl chloride, pyridine and Meldrum's acid[114] in dichloromethane yielded **221** as an orange red solid.* On refluxing **221** with an excess of 2-cyclohexen-1-ol, the ester **222** was obtained in 53% yield. The experiment was also repeated with bromoacetyl bromide to yield **223** in 42% yield.

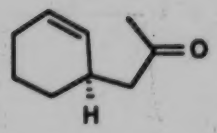
* ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.7 (s, 6H), 2.7 (s, 3H), 3.68 (s, 1H)



221



222 X= H; 223 X = Br



224

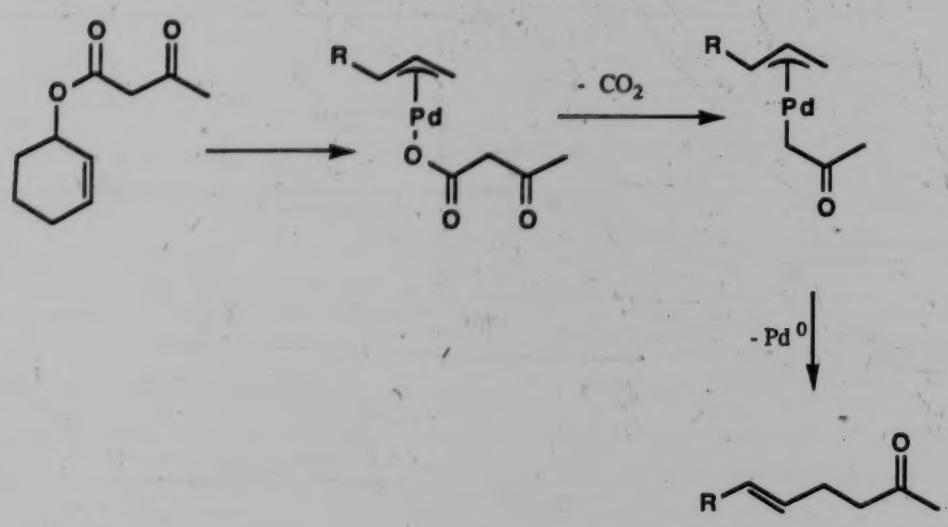
We then attempted the rearrangement of **222** to the ketone **224**. Heating of **222** in toluene at 190°C for 2 h (sealed tube) gave a small amount of **224**. Hill had not reported a yield for his rearrangement (eq 11) and close examination of the literature revealed an article by Burgstahler[115] in which the attempted thermal rearrangement of the ester **222** was described as part of an investigation into the Claisen rearrangement of cyclic substrates. Burgstahler observed that heating ester **222** (10 g) at 170-180°C for 2 h yielded carbon dioxide (1250 mL), acetone (2.3 g), 1,3-cyclohexadiene (1.5 g). Ketone **224** (0.45g as the semicarbazone) was isolated from the residue. Obviously the major thermal reaction for cyclic substrates is not rearrangement, but elimination.

Thus, we explored the possibility of effecting the rearrangement under milder conditions. Tsuji[116] has reported the palladium(0)-mediated rearrangement of allylic 3-oxobutanoates (Scheme 12). We attempted to apply this reaction to **222**, but with little success. We were able to isolate only a small amount of the crude ketone **224**. The intermediacy of an unsymmetrical π-allyl palladium complex (arising from an

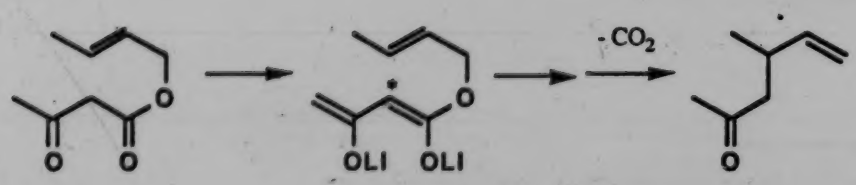
unsymmetrically substituted olefin) would result in the formation of regioisomeric products.

Another method for effecting the Carroll rearrangement under mild conditions was described by Wilson.[117] The dianions of allylic 3-oxobutanoates, generated with lithium diisopropylamide, undergo clean rearrangement to β-keto acids which can be decarboxylated by refluxing in carbon tetrachloride (Scheme 13).

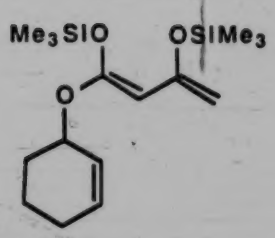
Scheme 12



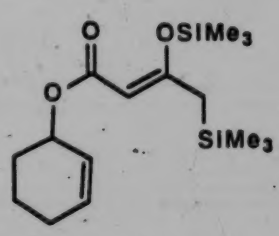
Scheme 13



Wilson suggested that the reaction of the dianion occurs under mild conditions due to the increased electron density at the reactive center (see starred atom in Scheme 13). However, a number of attempts at deprotonation and subsequent rearrangement were unsuccessful. It seemed reasonable, therefore, to prepare the disilyloxy butadiene **225**, trapping the lithium dienolate that Wilson suggested as a possible intermediate.

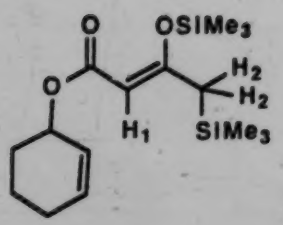


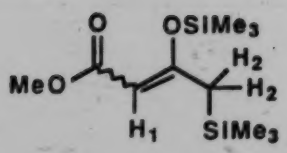
225



226

In our first attempt to make **225**, the ester **222** was sequentially treated with sodium hydride (1.2 equiv.), n-butyllithium (1.1 equiv) and chlorotrimethylsilane (2.0 equiv.) in THF at O°C. A single product was obtained in 59% yield. The material was thermally stable. Heating for 20 h at 75°C in toluene did not change the spectral characteristics, and we later assigned the structure as **226** based upon literature values for the known analogue **227**.[118]

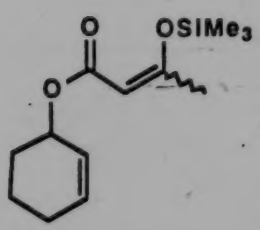


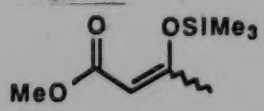


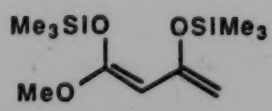
226 H_1: δ 5.00, H_2: δ 1.44

227 (E) H_1:δ 4.95 and H_2: δ 2.42,
(Z) H_2: δ 1.67.

In the second approach to butadiene **225**, we first prepared the 3-trimethylsilyloxy-2-butenaote **228** according to a method described by Danishefsky.[119] The allylic 3-oxobutanoate **222** (0.5 equiv.) was added to a suspension of anhydrous zinc chloride (3 mol%) in triethylamine (1.0 equiv.) and benzene. Chlorotrimethylsilane was added and the mixture was stirred overnight. Distillation yielded **228** as a mixture of isomers (E:Z::2:1) in 82% yield. The ^{1}H NMR properties of **228** compared well with those of **229**.*





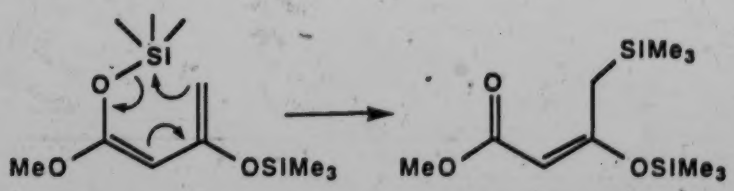


228 **229** **230**

Ester **228** was also thermally stable. Deprotonation of **228**[120] with lithium diisopropylamide in the presence of TMEDA (N,N,N',N'-

* **228**: ^{1}H NMR ($CDCl_3$):δ (=CH) 5.06 and 5.04 , (=CMe) 2.26 and 1.90 (integrate 2:1), **229**;^{1}H NMR ($CDCl_3$):δ (=CH) (Z) 5.10 and (E) 5.14, (=CMe) (Z) 1.90 and (E) 2.27.

tertramethylethylenediamine), and quenching of the resulting dienolate with chlorotrimethylsilane, yielded **225**. The NMR properties of **225** compared favorably with those of **230**.[118]** Distillation of the crude butadiene gave an oil which, when hydrolyzed (Bu_4NF, aqueous THF), gave **224** (ca. 20%) and the β-keto ester **222** (ca. 40%). After completiion of this work, it came to our attention that the butadiene **225** will undergo a thermal 1,5 silicon shift from O to C (equation 12).[118]

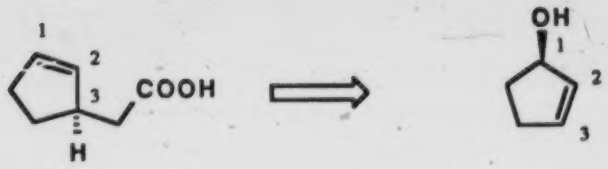


eq 12

Due to its thermal lability, it seemed unlikely that we would be able to effect rearrangement of **225** in synthetically useful yields

We next turned our attention then to the use of 2-cycloalken-1-yl acetic acids, for example **231**. Such acids could be derived form the appropriate allylic alcohols via the well-studied Claisen rearrangement.[121,122] The suprafacial nature of this rearrangement means that the stereochemistry of the ester at C-3 is predictable with proper choice of stereochemistry at C-1 in the starting allylic alcohol.

** 225: ^1H NMR ($CDCl_3$): δ (=CH_2) 3.94, 4.10 (=CH-C) 4.44, 230 ($CDCl_3$) δ (=CH_2) 3.94, 4.13 (=CH-C) 4.45.

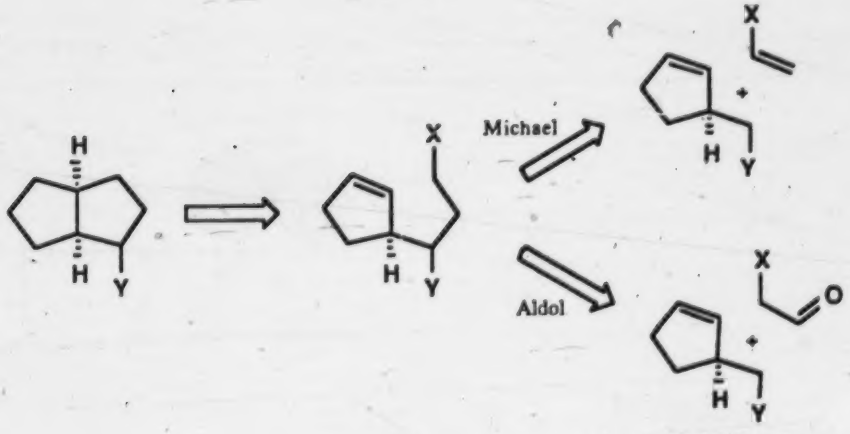


231

Compounds such as **231** could be subjected to aldol or Michael reaction in order to build up a new five-membered ring (Scheme 14).

We decided to pursue the possibility of an aldol reaction between (phenylseleno)acetaldehyde and the enolates of the esters of the 2-cycloalken-1-yl acetic acids. We were also interested in the ring-fusion stereochemistry obtained upon radical cyclization.

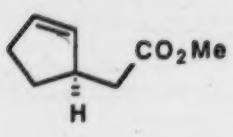
Scheme 14.



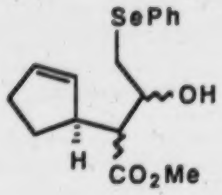
[For example **Y** = ester, aldehyde ; **X** = SePh, SPh, halide]

Compound **232** was prepared in 60% yield by esterification ($MeOH/ H_2SO_4$) of the commercially available acid **231**. Deprotonation of the ester with LDA gave the

ester enolate. This was quenched with (phenylseleno)acetaldehyde[123] to afford the β-hydroxy esters **233** (as a mixture of isomers) in 40% yield. Silyl ketene acetal **234*** was also prepared but reaction of this with (phenylseleno)acetaldehyde in the presence of titanium(IV)chloride[124] at -78°C yielded **233** in only 34% yield. It was found that, if the (phenylseleno)acetaldehyde was chromatographed, distilled and used directly, the yields were much improved in the aldol reaction. Addition of freshly purified (phenylseleno)acetaldehyde (1.25 equiv.) to the lithium enolate of **232** in THF at -78°C, followed by acetic acid (1.5 equiv. in THF) gave the β-hydroxy esters **233** in a yield of 71%.



232



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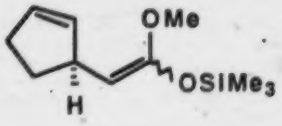


234

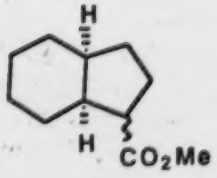
Although it was not our original intention, we examined the cyclization of **233** with triphenylstannane. The bicyclic product **235** was produced as a mixture of isomers (49:27:10:14) in 90% yield. Two other examples of this cyclization were investigated and the results are portrayed in Table 7.

---

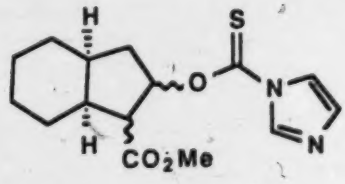
*Prepared by addition of chlorotrimethylsilane (3.0 equiv.) to the enolate of **232** [prepared by deprotonation of the ester with LDA (1.1 equiv) at -78°C] and warming to room temp (1 h). Distillation (85°C, 15 mm) yielded **234** (75 %): IR 1685 cm^{-1}.

Ester **236*** was prepared in 80% yield in a similar manner to ester **232**. Deprotonation and quenching of the enolate with (phenylseleno)acetaldehyde gave the β-hydroxy esters **237**, again as a mixture of four diastereoisomers (44:40:10:6). The β-hydroxy esters were then cyclized to the octahydroindenes **238** in 91% yield. We were able to determine the ring junction stereochemistry by deoxygenation of **238** to the known esters **242**[126] via the imidazolides **243**.[127]

Thus, **238** was refluxed with thiocarbonyldiimidazole in dichloromethane for 12 h to give imidazolides **243** in 96% yield. The imidazolides and AIBN (catalytic amount) were added slowly to a refluxing solution of tributylstannane in THF. The esters **242** were isolated in 81% yield. The ^{13}C NMR spectrum of the epimeric esters correlated with that of an authentic mixture.



242

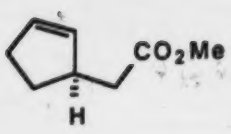


243

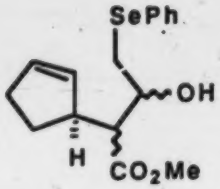
* Prepared from 2-cyclohexen-1-yl acetic acid[125] (reflux MeOH, H_2SO_4: cat 80%).

Table 7

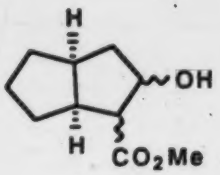
Aldol reaction of 2-alken-1-yl acetates and cyclization of the β-hydroxy esters.



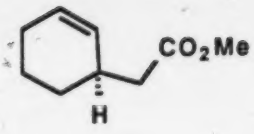
232



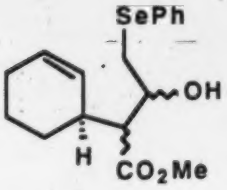
233 (71%)



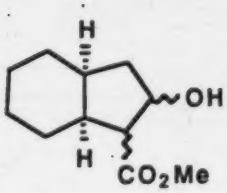
235 (90%)



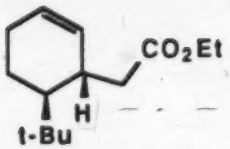
236



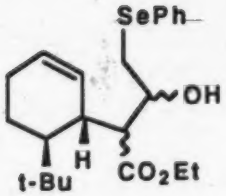
237 (84%)



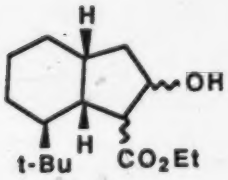
238 (91%)



239



240 (94%)



241 (71%)

We wanted also to examine an example where the pendant side chain was held in a pseudo-equatorial conformation, at least in the ground state. Ester **239** fitted our needs. In order to prepare **239** (via Claisen rearrangement) it was necessary to obtain isomerically pure trans-4-tert-butyl-2-cyclohexen-1-ol **244**. Ketone **245** was made in 3 steps from 4-tert-butylcyclohexanone (Aldrich).[128] Reduction of **245** with aluminum tri(2-propanolate) in 2-propanol gave a mixture of **244** and the isomer **246** in a 78:22 ratio and in 96% yield.* The isomer mixture was esterified with p-nitrobenzoyl chloride in pyridine at room temperature to afford a mixture of the p-nitrobenzoates.[129]

244

245

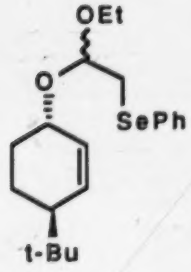
246

Two recrystallizations from methanol, yielded the isomerically pure trans-benzoate. Hydrolysis with potassium hydroxide in aqueous methanol then gave **244** in 93% yield (from the benzoate). The isomeric purity of the alcohol was checked by ^{1}H NMR, thin layer chromatography and VPC analysis. A small amount of **244** was hydrogenated using Adams catalyst in ethanol at room temperature to yield trans-4-tert-butylcyclohexanol. The ^{13}C NMR spectrum of this material compared favorably with

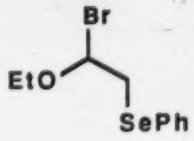
* ^{1}H NMR (200 Mhz, $CDCl_3$): δ t-Bu signals **244** (trans) 0.87 and **246** (cis) 0.91.

literature values[130] and served to differentiate it, and hence **244**, from the cis isomer. A pure sample of cis-4-tert-butylcyclohexanol was also examined by ^{13}C NMR.* It was now necessary to prepare the ester **239** by Claisen rearrangement. The method used was one outlined by Petrzilka.[122]

Following his procedure, the acetal **247** was prepared by treatment of **248** (generated in situ from ethyl vinyl ether and phenylselenenyl bromide) with a mixture of **244** and diisopropylamine. This reaction proceeded in 90% yield.



247



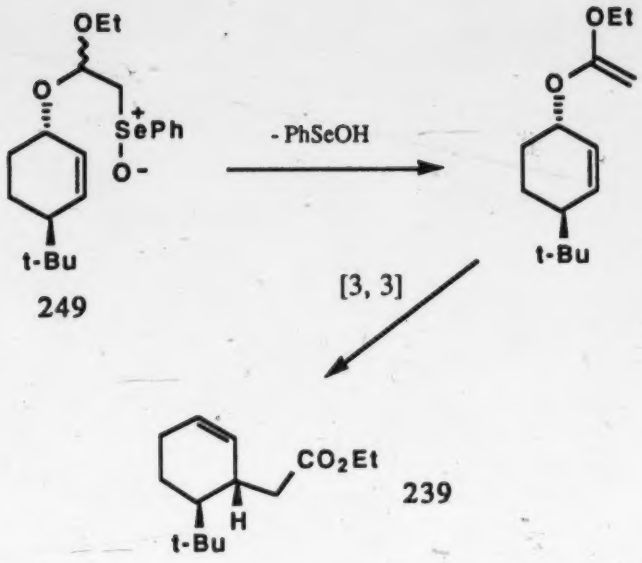
248

Oxidation of **247** with sodium metaperiodate in basic aqueous methanol yielded the selenoxide **249**. This was then immediately dissolved in chlorobenzene with n-hexylamine and the solution was refluxed for 18 h to yield the crude ester **239**. The reaction proceeds via selenoxide elimination (Scheme 15) to give the vinyl ether, which then rearranges under the thermal conditions to ester **239**; the stereochemistry of the product is a result of the suprafacial nature of the rearrangement.[131]

---

* trans-4-tert-Butylcyclohexanol (100.6 MHz, $CDCl_3$) δ 25.7, 27.7, 32.3, 36.2, 47.4, 71.1. cis-4-tert-butylcyclohexanol: δ 20.9, 27.5, 32.6, 32.4, 48.1, 66.0

Scheme 15



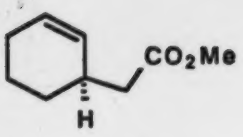
Chromatography and distillation of the crude ester provided an analytically pure sample of **239** in 56% yield (from the selenide **247**).

The lithium enolate of ester **239** reacted smoothly with (phenylseleno)acetaldehyde to yield the β-hydroxy esters **240**. Cyclization of **240** with triphenylstannane produced the octahydroindenes **241** as a mixture of two major isomers in 74% yield. The isomers could be partially separated by careful chromatography. Double resonance experiments allowed the low field signals of the ^{1}H NMR spectra to be assigned for each isomer. The cis-ring-fusion stereochemistry was established for each isomer by Nuclear Overhauser difference experiments. Upon irradiation of either ring junction proton, the other showed an enhancement of 6.5-8%.

Our results show that the method allows efficient formation of cis-ring-fused bicyclo[3.3.0]octanes and bicyclo[4.3.0]nonanes. The mildness of the radical step circumvents the need for functional group protection.

We now returned to our initial aim of studying α-keto radicals. We investigated a number of routes for the preparation of suitable precursors to α-keto radicals, as described below. We finally settled for the obvious method employing classical chemistry.

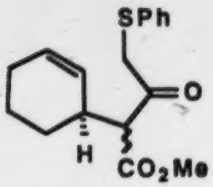
In the light of the experiments just described we were attracted to the possibility of making the precursors to the α-keto radicals by acylation of (2-cycloalken-1-yl)acetates. Direct acylation of the ester enolates with an appropriate α-substituted acid chloride should give the desired radical precursor. Several experiments revealed that deprotonation of the esters (**232** and **236**) with lithium diisopropylamide and addition of chloroacetyl chloride, bromoacetyl bromide, or (phenylseleno)acetyl chloride was not successful. A problem in these particular acylation reactions was that the product was a β-keto ester ($pK_a \equiv 11$), which is far more acidic than the ester ($pK_a \equiv 24.5$). Therefore, deprotonation of the product occurs at a faster rate than acylation of the ester enolate. We adopted a procedure originally developed by Rathke[132] for acylation of esters. He circumvented the problem of product deprotonation by using 2 equivalents of the hindered base, lithium N,N'-diisopropylcyclohexylamine (LiICA). Deprotonation of ester **236** with LiICA in THF at -78°C, and addition of (phenylthio)acetyl chloride **250** failed to yield any of the desired β-keto ester **251**.



236

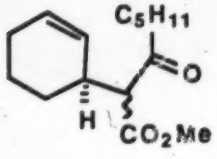
$PhSCH_2COCl$

250

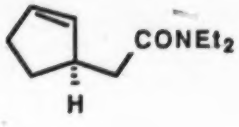


251

With n-hexanoyl chloride the ester **236** was acylated under similar conditions to give β-keto ester **252** in 54% yield. This moderate yield is expected from the values given in Rathke's article. Another problem that might be encountered is deprotonation of the acid chloride rather than acylation, due to the increased acidity of the α-protons in the α-substituted acid chlorides. We also examined the amide **253***; however, we could not acylate its lithium enolate with (phenylthio)acetyl chloride.



252

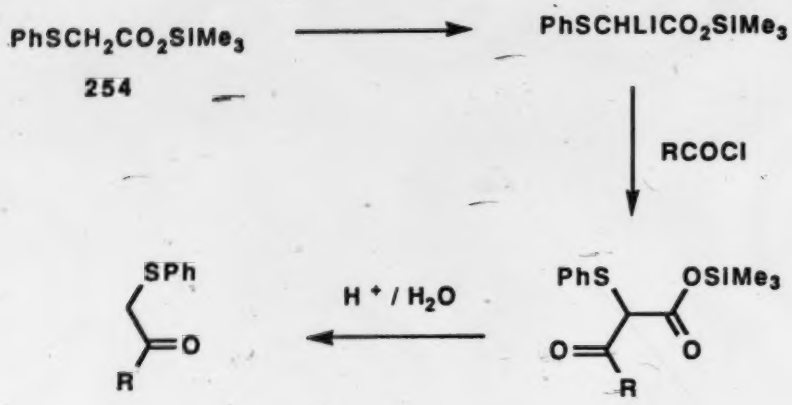


253

Another possibility involved the use of the lithium enolate of trimethylsilyl (phenylthio)acetate **254** (Scheme 16).

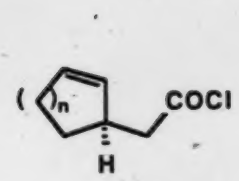
* Prepared in 82% yield from acid chloride **255** by reaction with diethylamine: bp 82-85°C (0.2 mm).

Scheme 16



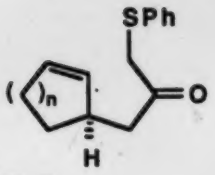
The silyl ester **254** was prepared by stirring (phenylthio)acetic acid[133] with hexamethyldisilazane (0.75 equiv.) and chlorotrimethyl silane (0.3 equiv.) in pyridine for 12 h. The reaction yielded **254** as a colorless, distillable liquid in 74% yield. This was deprotonated with LiICA at -78°C in THF and acid chloride **255*** was then added. After 10 min the reaction was quenched (acetic acid). The residue was dissolved in dioxane, made acidic with aqueous hydrochloric acid, and heated for 15 min to effect decarboxylation of the intermediate β-keto ester. The residue afforded crude **256** in 56% yield. Purification proved difficult and only a 30% yield of pure **256** was isolated. Repetition of the experiment with acid chloride **257** was also inefficient, yielding crude **258** in 59% yield. The material defied purification using chromatographic techniques.

* Compounds **255** and **257** were prepared from the acids **231** and 2-cyclohexen-1-yl acetic acid[125] respectively each in 84% yield (oxalyl chloride, benzene, room temp, 2 h).



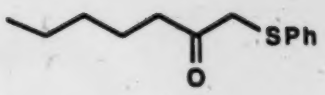
255 n = 1

257 n = 2



256 n = 1

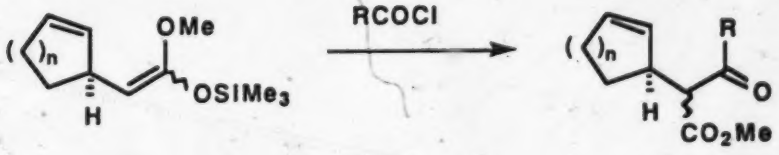
258 n = 2



259

A similar experiment performed using n-hexanoyl chloride produced the α-(phenylthio)methyl ketone **259** in only 39-40% yield. Similar experiments using trimethylsilyl (phenylseleno)acetate likewise were unsuccessful. We also used the dianion of (phenylthio)acetic acid; however, reaction with acid chloride **255** gave ketone **256** in only 28.5% purified yield.

The above approach was clearly unpromising. Even if the yields could be optimized, the reaction products were generally difficult to purify. We also investigated the possibility of acylation employing silyl ketene acetals (equation 13).[134-136]

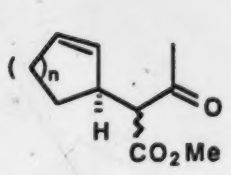


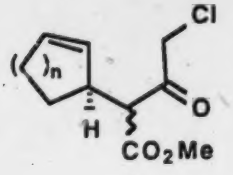
eq 13

234 n = 1 260 n = 2

We based our study on two literature reports involving (i) the reaction (equation 13) catalyzed by a zinc halide[135] and (ii) the use of triethylamine for the in situ generation (from the acid chloride) of a ketene, which then reacted with the silyl ketene

acetal.[136] The results of our investigation are listed in Table 8. The silyl ketene acetals **234** and **260** were prepared by quenching the lithium enolate, prepared from the appropriate ester (**232** and **236**) in THF -78°C, with chlorotrimethylsilane, in 88% and 84% yields, respectively. The silyl ketene acetals were stored under dry conditions to prevent hydrolysis and periodically checked for decomposition (^{1}H NMR). The acid chlorides used in the experiments were distilled prior to use.





261 n = 1 **262** n = 2 **263** n = 1 **264** n = 2

Table 8

Reactions of silyl ketene acetals with acid chlorides.

Entry	SKA[c]	Method[d, e]	Y[b]	cat	Prod.	yield%[a] 1	2
1	234	A	H	$ZnCl_2$	261	38	46
2	234	A	Cl	"	263	41	53
3	260	B	H	"	262	44	55
4	260	B	H	$ZnBr_2$	262	39	54
5	260	C	Cl	"	264	33	45
6	260	C	SPh	"	251	31	35
7	260	D	SPh	"	251	45	66
8	260	E	H	N/A	262	54	59
9	260	E	Cl	N/A	264	51	65
10	260	E	SPh	N/A	251	43	51

[a] Yield 1 refers to isolated yield, 2 refers to yield adjusted for recovery of esters. [b] Y in YCH_2COCl. [c] Silyl Ketene Acetal. [d] All reactions were quenched with dilute aqueous HCl.

[e] Method:

A Add silyl ketene acetal to stirred sol of ZnX_2 (10 mol%) and acid chloride in CH_2Cl_2 at room temp.

B As A, except, 2 equivalents of acid chloride were used.

C As A, except that CCl_4 was used as solvent.

D As A, except inverse addition was used, i.e. acid chloride (1.25 equiv.) was added to silyl ketene acetal.

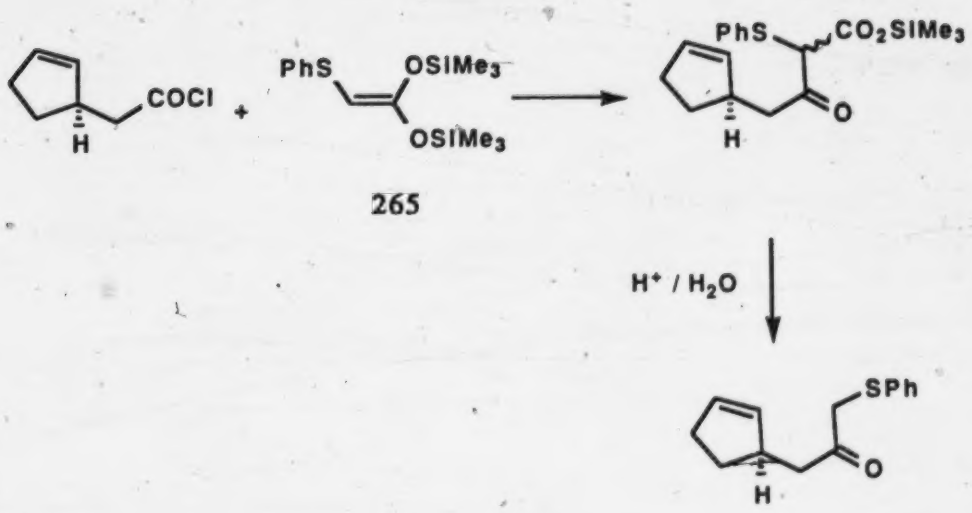
E Acid chloride (1.1-1.2 equiv.), silyl ketene acetal THF, 0°C. Add triethylamine (1.05 equiv.), stir 1 h, then 2h at room temp.

All the reactions were quenched with dilute acid prior to isolation of the products. The yields of the products were determined taking into account the amount of ester **232** and **236** recovered. This was necessary to avoid discrepancies in the yield due to i) an incomplete reaction or ii) inadvertent side reactions involving cleavage of the silyl ketene acetal (for example with traces of hydrochloric acid).

Unlike the acylation reactions, the success of these reactions is not sensitive to the nature of the acid chloride. The use of THF as a solvent was not successful and simply heating the reactants together in dichloromethane was also ineffective. The use of an excess of acid chloride did not have any marked effect (entries 1 and 2 vs. 3 and 4); also zinc chloride and zinc bromide were equally effective (entries 3 and 4). The use of dichloromethane was clearly better than carbon tetrachloride (entries 5 and 6). The best yields were obtained when the ketene was generated in situ and allowed to react with the silyl ketene acetal (entries 8, 9 and 10). Inverse addition (entry 7) was also effective. The reaction resisted attempts at improvement and the yields were consistently moderate.

We also explored the possibility of an approach using silyl ketene acetals based on a report by Wissner (Scheme 17).[134]

Scheme 17



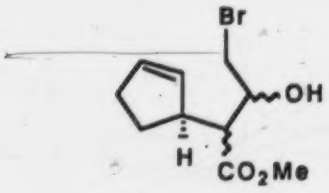
The silyl ketene acetal **265** was prepared from trimethylsilyl (phenylthio)acetate **254**. Treatment of **254** with lithium hexamethyldisilazide and chlorotrimethylsilane yielded a mixture of **265** and **266** in a ratio of 76:24 [a small amount (<5%) of the starting ester **254** was also present]. It was not possible to separate the two products by distillation and their identities and ratios were assigned on the basis of spectral data obtained on the mixture.

$PhSCH_2CO_2SiMe_3$	$PhSCH(SiMe_3)CO_2SiMe_3$	$PhSCH{=}C(OSiMe_3)_2$
254	**266**	**265**
δ (CH_2) 3.62	δ (CH) 3.48	δ (=CH) 4.33
1705 cm^{-1}	1675 cm^{-1}	1605 cm^{-1}

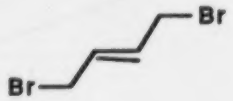
The occurrence of some C-silylation is in contrast to Wissner's observation with $MeSCH_2CO_2SiMe_3$, which gave 100% O-silylation. It is quite probable that the phenylthio group stabilizes the negative charge on the adjacent carbon to a greater extent

than the methylthio unit. The ketene acetal **265** (4.0 equiv. as a mixture with **266**.) was refluxed with acid chloride **255** for 16 h in chlorobenzene. Hydrolysis (heat, H^+/dioxane) and isolation gave **256** in only 44% yield (see Scheme 17).*

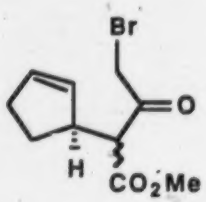
We also attempted to oxidize the β-hydroxy esters prepared previously. The γ-bromo-β-hydroxy esters **267** were made in 68% yield by reaction of the enolate of ester **232** with anhydrous bromoacetaldehyde. This was available by ozonolysis of (E)-1,4-dibromo-2-butene **268**.**[137]



267



268



269

Swern oxidation[139] of **267** yielded a single product with the ^1H NMR characteristics expected for **269**. An analytically pure sample could not be obtained and the ^{13}C NMR spectrum showed the presence of impurities. Oxidation with Collins reagent ($CrO_3{\cdot}Py_2$) was not successful.[140]

The oxidation of the corresponding γ-(phenylseleno)-β-hydroxy esters such as those listed in table 7 faced two problems. Mild conditions are necessary for the

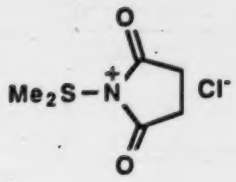
---

* Wissner reported that S-acylation was a side reaction.

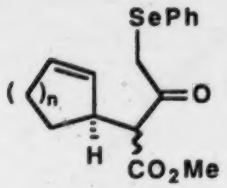
** Prepared by reaction of bromine with 1,3-butadiene: mp 53-54°C (lit.[138] mp. 52.5 °C)

oxidation of β-hydroxy selenides to prevent oxidation of the selenium and possible eliminative pathways. Also β-hydroxy esters are sensitive to some oxidizing reagents due to the occurrence of a number of side reactions, for example, fragmentation (retro-aldol reaction), the elimination of water and further oxidation of the enol tautomer of the product β-keto ester.[141]

A number of methods are available in the literature for oxidation of β-hydroxy selenides.[142-145] Swern oxidation (appropriate for the oxidation of β-hydroxy esters[141]) was ineffective with these substrates. The use of dimesityl diselenide and tert-butyl peroxide was reported to be successful.[142] Therefore **233** was added to a refluxing solution of dimesityl diselenide and tert-butyl peroxide in benzene. The β-keto esters **270** were isolated in only 47% yield. Barton[144] reported the use of triphenylbismuth carbonate as a mild oxidant, but yields of only ca. 45% were obtainable. A method described by Petrzilka,[145] based on the Corey-Kim oxidant, **271**, proved to be more useful. The β-hydroxy esters **233** were added to a cooled solution of **271** [prepared from dimethyl sulfide and N-chlorosuccinimide] in dichloromethane. After a suitable time, triethylamine was added and isolation gave **270** in 75% yield. β-Hydroxy esters **237** were also oxidized in a similar manner to the β-keto esters **272** in 77% yield.

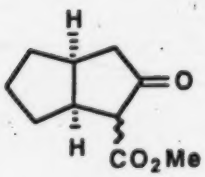


271

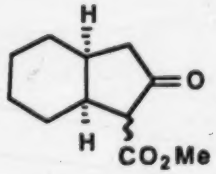


270 n = 1, 272 n = 2

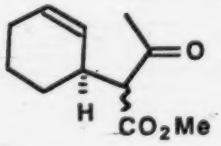
We were now in a position to attempt the proposed α-keto radical cyclizations. Both **270** and **272** were smoothly cyclized with triphenylstannane (1.25-1.3 equiv.) to the bicyclic β-keto esters **273** and **274** in good yield. The cyclization of **272** resulted in the formation of some of the reduced ester **262** (arising from hydrogen abstraction from the stannane by the α-keto radical) along with the desired product **274**.



273 (80%)



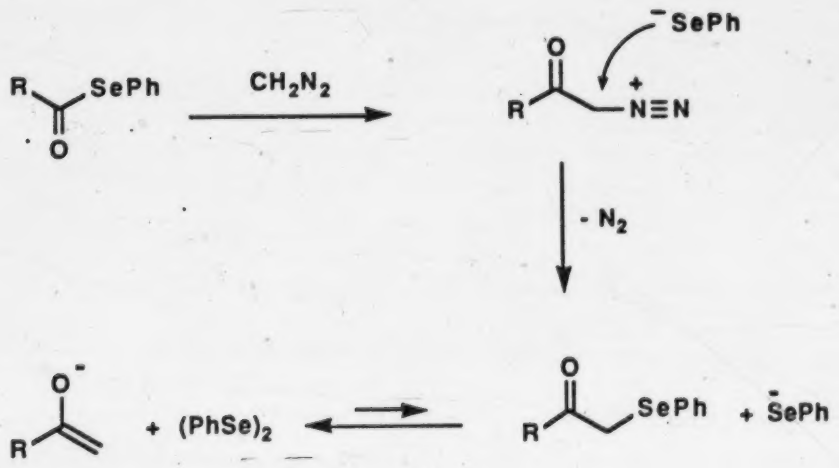
274 (70%)



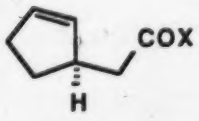
262 (9%)

At this stage we continued our search for a good method for synthesis of α-substituted methyl ketones. A report by Back[146] clearly merited our attention. He described the synthesis of α-phenylseleno methyl ketones by the insertion reaction of diazomethane with selenoesters (Scheme 18).

Scheme 18

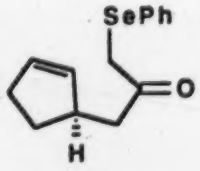


Methyl ketones are formed as a major side product due to the existence of an equilibrium between the methyl ketone enolate and the α-phenylseleno ketone. The equilibrium lies heavily toward the former compound. Even though this was not a synthetically viable route, we were still able to obtain sufficient amounts of the α-phenylseleno ketone to try the radical closure step. The seleno ester **275** was prepared in 90% yield by the reaction of the acid chloride **255** with benzeneselenol in the presence of pyridine. Stirring **275** with an excess of diazomethane at room temperature yielded the ketone **276** in 42% yield.



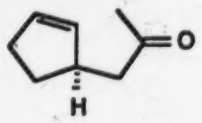
275 X = SePh

255 X = Cl

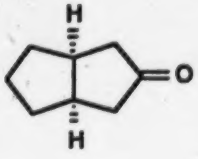


276

A solution of **276**, triphenylstannane (1.1 equiv.) and a catalytic amount of AIBN was refluxed in benzene for 1 h. Two products were isolated, **277** (63%) and **278** (4%).



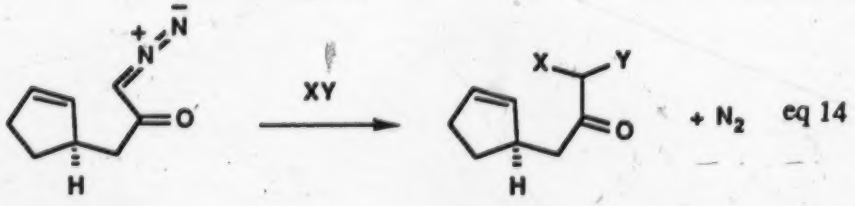
277



278

The identity of the bicyclic product was initially based upon its ^{1}H NMR spectrum. However, slow addition of triphenylstannane and AIBN to a refluxing solution of **276** in benzene resulted in a complete reversal of the product ratio yielding **277** and **278** in 10% and 64% yields respectively. Positive identification of **278** was then based on a comparison of its ^{13}C NMR spectrum with literature values.[147] Clearly α-keto radicals do cyclize and we continued our effort at finding a good route to the radical precursors.

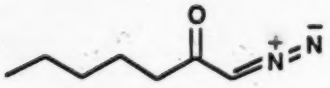
Based on a number of reports in the literature[148-150] we were attracted by the possibility of introduction of the required functionality via α-diazo ketones (equation 14).



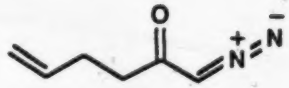
eq 14

279

The diazoketone **279** was prepared by addition of the acid chloride **255** to an excess of dry diazomethane. The reaction mixture was kept overnight at 3°C with protection from light. The excess of diazomethane was removed by stirring for a few minutes with silica gel at room temperature and then the diazoketone was isolated by evaporation of the solvent.* Unfortunately **279** did not react with a number of electrophiles: phenylselenenyl chloride, diphenyldiselenide (BF_3•Et_2O cat.) or iodine. Only complex mixtures resulted and the crude products displayed no signals (^1H NMR) characteristic of the desired products. In order to evaluate this failure, we studied two other diazoketones **280** and **281**.



280



281

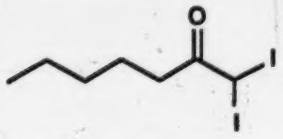
Compound **280** was prepared from n-hexanoyl chloride and **281** from 4-pentenoyl chloride, in a similar manner to **279**. In contrast to **279**, diazoketone **280** reacted cleanly with iodine. The addition of iodine (1.0 equiv.) to **280** (in an NMR tube) resulted in rapid decolorization and evolution of nitrogen. The ^1H NMR spectrum of the product was clean and consistent with the expected structure **282**.**

---

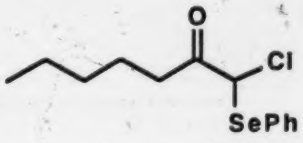
* Diazoketone **279** had: IR 2095, 1640, 1370 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ ($COHN_2$) 5.28 ppm.

** Compound **282** had: ^1H NMR ($CDCl_3$) δ 1.0 (t, 3.0H), 1.40 (m, 4H), 1.75 (m, 2H), 2.04 (t, 2H), 5.3 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ ($COCHI_2$) 13.9.

Diazoketone **280** also reacted cleanly with phenylselenenyl chloride (immediate decolorization and nitrogen evolution) to give **283** in 85% yield. The diazoketone **281** did not react cleanly with iodine, phenylselenenyl chloride or diphenyldiselenide, giving only complex reaction mixtures (TLC and ^{1}H NMR).

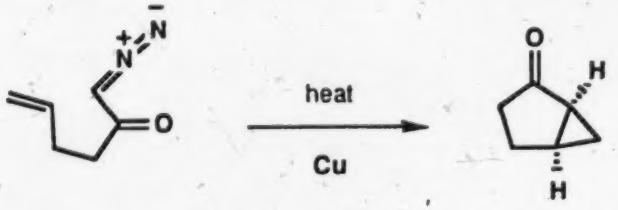


282



283

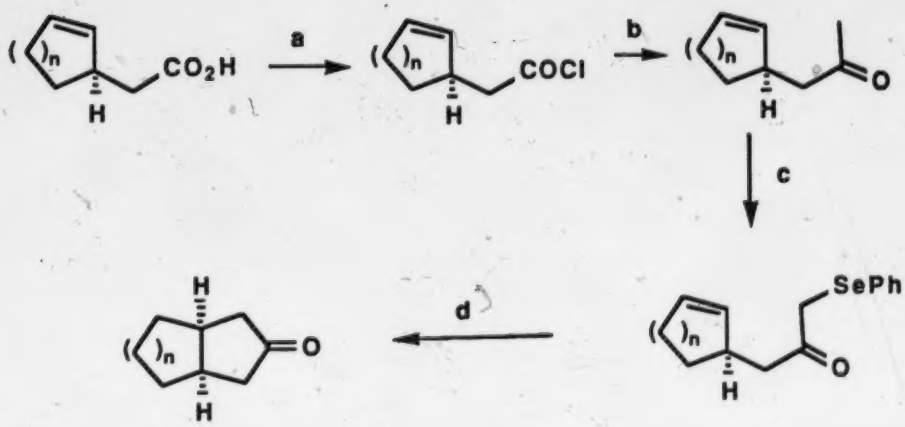
The only significant difference between the diazoketones **280**, **279** and **281** is the presence of unsaturation in the latter two. Diazoketone **281** will insert intramolecularly into the double bond (equation 15).[151]



eq 15

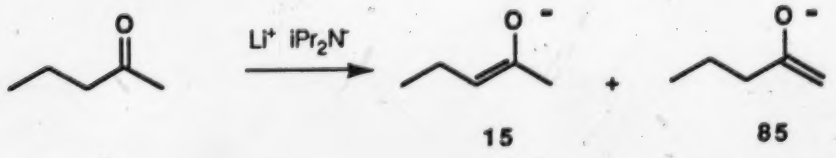
We finally adopted an approach using more classical methods (Scheme 19).

Scheme 19



a) oxalyl chloride, benzene r.t.b) Me_2CuLi, ethyl ether -78°C. c) i LDA, THF -78°C ii PhSeCl. d) Ph_3SnH, AIBN, benzene reflux. LDA = lithium diisopropylamide.

Our original reluctance to employ this approach was due to the possible formation of regioisomers from the kinetic deprotonation of the methyl ketones and subsequent reaction with phenylselenenyl chloride. We expected a ratio of products to be at least better than 85:15 based upon deprotonation studies with 2-pentanone (equation 16).[152]



eq 16

We decided to make use of dimethyl lithium cuprate (Me_2CuLi) to form the methyl ketone, rather than methyllithium, due to the mildness of the former reagent.

Also the yields, compared with those obtained by using methyllithium, are higher and there are no problems due to formation of the dimethylcarbinol as a side product.

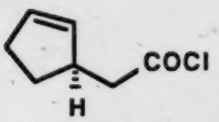
A number of methyl ketones were prepared from the appropriate acids via their acid chlorides (Table 9). Acids **285**[153], **287**[154] and **289**[155] were converted into their acid chlorides which were then used directly to prepare the methyl ketones **286**, **288** and **290**, respectively. The acid **287** was obtained by Diels-Alder reaction between 1,3-cyclohexadiene and 2-propenoic acid (sealed tube, 170°C, 24 h). Distillation of the product yielded the acid **287** as a mixture of endo and exo isomers (76:24) in 55% yield. The literature directions[154] specify 'several' recrystallizations from cold pentane (-30°C) to obtain the pure endo isomer. We were not able to purify the acid by this means beyond the stage at which it contained 93% of the endo isomer (^{1}H NMR),* and so we decided to separate the isomers at a latter stage. The acid chlorides were prepared by reaction of each of the acids with oxalyl chloride in benzene at room temperature. The acid chloride was then added to an ethereal solution of dimethyl lithium cuprate at -78°C. The reaction was quenched with methanol after a short time and the methyl ketones were isolated in the yields shown (Table 9).

---

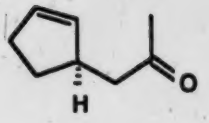
* ^{1}H NMR of **287**: δ (CH-CO_2H) endo 2.98 (bs), exo 2.88 (bs).

Table 9

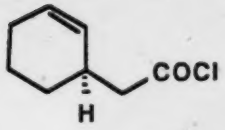
Preparation of 2-propanones.



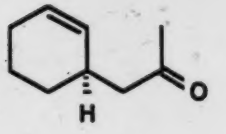
255 84%[a]



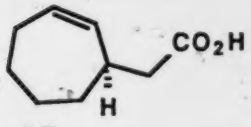
277 84%



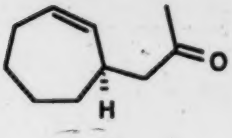
257 84[a]%



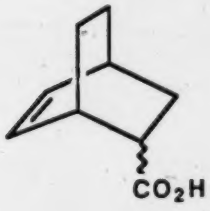
284 94%



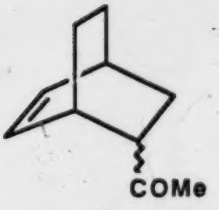
285



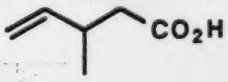
286 77%



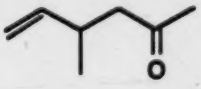
287 endo:exo 93:7



288 89% endo:exo 93:7



289



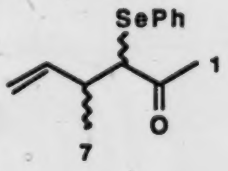
290 42%[b]

[a] Yield of acid chloride from acid. [b] Low yield due to volatility.

Fortunately, the phenyselenation of the methyl ketones proceeded with good regioselectivity (Table 10). The ketones were deprotonated by addition to a cold (-78°C) solution of lithium diisopropylamide in THF. Phenylselenenyl chloride was then added to afford the desired α-phenylseleno ketones. Each of the compounds exhibited a ^{1}H NMR signal for the methylene proton adjacent to the ketone at ca. δ 3.6. Based upon the NMR spectra we could not dismiss the possibility of contamination by <5% of the regioisomer. The yields in the reactions did not vary when either reagent grade PhSeCl, or recrystallized (hexane) material, or PhSeBr (sublimed) was used. A small amount of the α,α-bis(phenylseleno) ketone **296** was formed in the reactions.

296 $RCOCH(SePh)_2$

In the case of methyl ketone **290** we observed approximately 10.5% of the regioisomer **295** along with the desired compound **294**. The presence of **295** was based upon the ^{1}H NMR spectrum. Since **295** is present as two diastereoisomers we would expect to see two singlets for H-1 and two methyl doublets (one for each diastereoisomer) for H-7.*

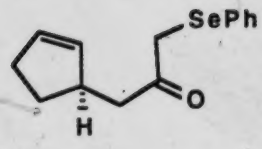


295

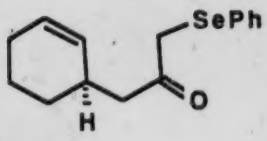
* Compound **295** (^{1}H MNR, $CDCl_3$) for H-7 δ 1.06 and 1.25 (d); for H-1 δ 2.24 and 2.20 (s)

Table 10

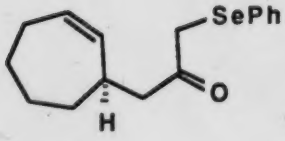
Preparation of α-phenylseleno ketones.



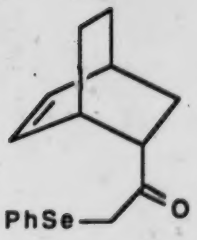
276 69%



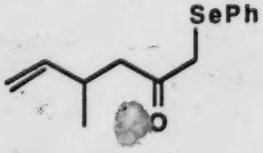
291 72%



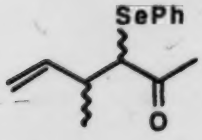
292 75%



293 67%



294



295

89.5:10.5 68% total.

We found that the α-phenylseleno ketone **293** could be separated from its exo stereoisomer by careful column chromatography.

Slow addition of triphenylstannane to a refluxing solution of the α-phenylseleno ketones afforded the cyclized compounds (Table 11). In all cases the cyclized product could be separated from the methyl ketone. We always obtained some of the methyl ketone (except with selenide **293**) resulting from reduction of the α-phenylseleno ketone. It is possible to reuse the recovered methyl ketone. In separate experiments for α-phenylseleno ketones **276**, **291** and **292**, the reaction mixtures were analyzed by VPC and the ratio of reduced product to cyclized product was determined (Table 12).

Table 12

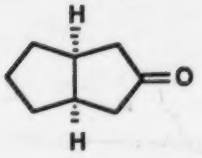
Reaction products of cyclizations.

Ketone	Products	Cyclized:Reduced
276	**278:277**	84:16
291	**297:284**	84:16
292	**298,299:286**	79:21

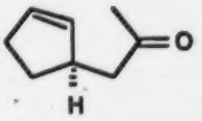
The cyclized products **278**[147] and **297**[156] were identified by comparison with the published ^{13}C NMR spectral data. The bicyclic product **298** was a mixture of cis- and trans-ring-fused isomers. The ^{13}C NMR spectrum of the cyclized material showed a number of small peaks which were not consistent with the structures of cis- or trans-**298**, or methyl ketone **286**.

Table 11

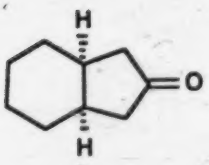
Cyclization of α-phenylseleno ketones.



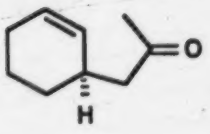
278 65%



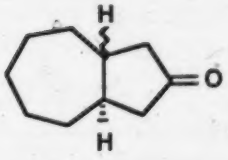
277 5%



297 71%

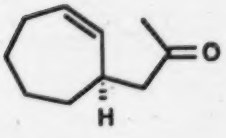


284 11%

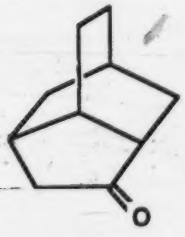


298 68%[a]

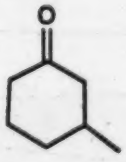
299 5%[b]



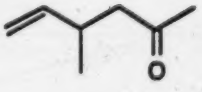
286 15%



300 86%



301 76%[c]



290 10.5%[d]

[a] A mixture of cis- and trans- isomers. [b] Inseparable (chromatography over silica gel) from cis- and trans- **298**. [c]Determined by VPC analysis. [d]Determined from DNP derivative of mixture **301** and **290**.

They were identified as belonging to bicyclo[4.3.1]decan-8-one **299**.[157] The ^{13}C NMR data quoted in the literature, along with our spurious signals are presented below (Table 13).

Table 13

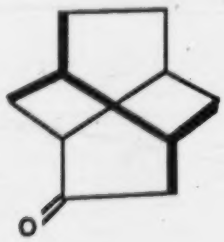
NMR data for bicyclo[4.3.1]decan-8-one.

	^{13}C ($CDCl_3$)	299 ($CDCl_3$)
3,4	26.0	26.0
2,5	31.3	-
10	34.7	34.7
1,6	35.2	35.2
7,9	48.5	48.4
8	207.1	-

The structure of compound **300**, obtained from the reaction of α-phenylseleno ketone **293**, was based upon the following evidence. The presence of a cyclic ketone was indicated by the appearance of a strong $(M-42)^+$ peak in the mass spectrum of **300**, indicating the elimination of ketene. Also the ^1H NMR spectrum of **300** contained an ABX signal for the methylene protons adjacent to the ketone (J_{AB} = 18 Hz). There was a possibility that the product was **302**, tricyclo[4.4.0.$0^{3,8}$]decan-4-one (4-twistanone), arising from 6-endo closure. There is a clear difference in the ^{13}C NMR data for the two compounds,* particularly for the chemical shift of the carbonyl

* ^{13}C NMR data for tricyclo[4.4.0.$0^{3,8}$]decan-4-one (see ref. 158): δ 22.9, 24.5, 25.8, 27.2, 30.1, 31.8, 43.0, 46.7, 212.1.

carbon. For 4-twistanone (302) the shift is δ 212.1 and for 300 it is δ 222.5. Both spectra were recorded in deuterated chloroform. We conclude that our product is tricyclo[4.3.1.$0^{3,7}$]decan-5-one (5-isotwistanone) 300.



302

Surprisingly, the major product from reaction of α-phenylseleno ketone 294 were not the expected cis- and trans-3,4-dimethylcyclopentanones but 3-methylcyclohexanone 301. The yield, determined by VPC analysis using authentic 3-methylcyclohexanone as a calibration standard, was found to be 76 ± 2%. Isolation of ketone 301 proved difficult and so the 2,4-dinitrophenylhydrazone (DNP) derivative was isolated instead. The authentic DNP derivative was also prepared and the spectral and chromatographic characteristics of the two were very similar. The ^{1}H NMR spectrum of the DNP derivative indicated the presence of ca. 10.5% of the derivative of ketone 290. Thus, since the α-phenylseleno ketone used in the reaction was a mixture of 294 and 295 (in a ratio of ca. 89.5:10.5) it appears that very little reduction of the radical derived from 294 occurs, and the major pathway under our reaction conditions is 6-endo closure.

We also attempted to cyclize the α-phenylseleno ketones using tributylstannane and tributylgermane to see if the amount of methyl ketones obtained could be minimized. The results of these experiments are illustrated below (Table 14). α-Phenylseleno ketone **291** was used to test the hydrides, which were distilled prior to the experiment.

Table 14

Effect of different metal hydrides on cyclization

stannane	reduced:cyclized	yield
Ph_3SnH	14:86	85%
n-Bu_3GeH	36:64	85%
n-Bu_3SnH	20:80	84%

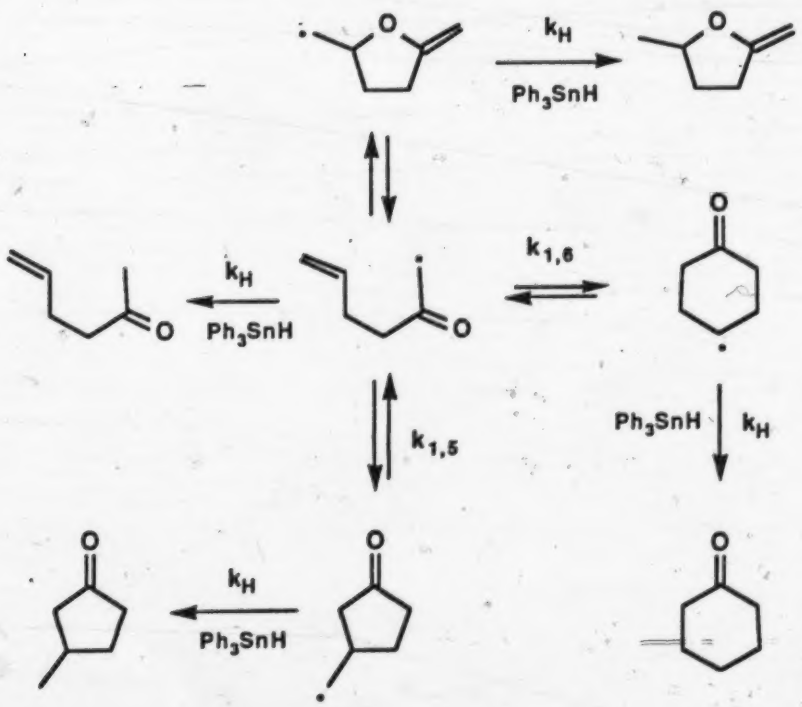
The ratios were determined by VPC analysis of the combined reaction products. The ^1H NMR spectra are in agreement with these values. It is interesting that tributylgermane gave a higher yield of the reduced product, considering that this reagent has been reported to be a poorer hydrogen donor than the stannanes.[159]

In principle, a number of processes could be involved in the cyclization of the α-keto radicals (Scheme 20).

It appeared that there was no serious barrier to ring closure via carbon for radicals such as **217**. We investigated the possibility of a rapid ring closure and opening via oxygen to give the radical **217**. Oxygen centered radicals do undergo

intramolecular addition reactions with a rate 2 to 3 orders of magnitude higher than that of a similar carbon centered radical.* In order to investigate this possibility we wanted to prepare the cyclic enol ether **305**. This compound would allow us to assess the reversibility of the process. We planned to synthesize **305** according to Scheme 21.

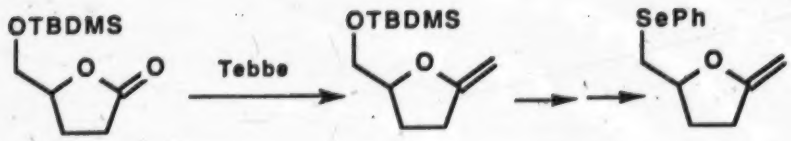
Scheme 20



The symbols $k_{1,5}$, $k_{1,6}$ and k_H refer to the processes of 5-exo ring closure, 6-endo closure and hydrogen abstraction, respectively.

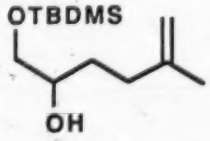
The pent-4-en-1-oxy radical undergoes 5-exo closure with $k_c > 10^8\ s^{-1}$ (25°C):[160] the hex-5-en-1-yl radical has a $k_c = 1 \times 10^5\ s^{-1}$ (25°C). [161]

Scheme 21



303 304 305

The lactone **303** was prepared from L-glutamic acid[162] and silylated with tert-butyldimethylsilyl chloride (TBDMS) according to Corey's general procedure.[163] However, several attempts to react **303** with the Tebbe reagent,* failed to produce **304** but gave instead **306** as the major product (48%).**



306

We turned our attention to **307** as a model substrate. Compound **307** was prepared from the β-ketoester **308**** using a procedure outlined by Ley.[165] The addition of N-(phenylseleno)phthalimide[166] to a stirred solution of **308** and a catalytic

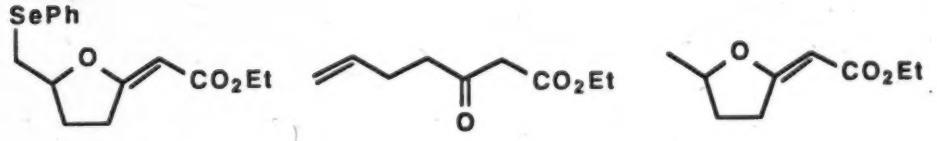
---

* [Bis(cyclopentadienyl)titanium](μ-chloro)(μ-methylidene)dimethyl aluminum., made according to procedure outlined in ref. 164.

** Compound **306**: ^{1}H (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.09 (s, 9H), 2.52, (m, 2H), 1.73 (s, 3H), 2.12 (AB, m, 2H), 2.52, (bs, 1H, CH-OH), 3.42, (m, 1H), 3.60 (m, 2H), 4.71 (d, J = 6.5 Hz, 2H); IR (OH) 3440 cm^{-1}; exact mass m/e 229.1624, (Calculated for $C_{12}H_{25}O_2Si$, m/e 229.1624).

*** Prepared from allyl bromide and ethyl 3-oxobutanoate according to a procedure outlined by Weiler (ref. 167) in 79% yield.

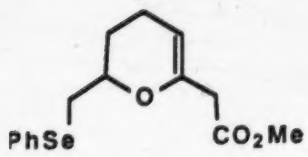
amount of iodine in dichloromethane gave the tetrahydrofuran **307** in 55% yield.* When **307** was treated with triphenylstannane under our slow addition conditions (i.e., the same conditions as used in the cyclization reactions), the reduced tetrahydrofuran **309** was obtained in 80% yield. None of the β-keto ester **308** was detected by VPC analysis. We were concerned that the conjugated double bond present in **307** might detract from its use as a valid model for **305**. Efforts to modify the ester by reduction of **307** ($LiAlH_4$, $LiHBEt_3$) or by reaction with an organometallic reagent (MeLi, MeMgBr) were unsuccessful, producing instead only polar products (presumably as a result of ring cleavage).



307 **308** **309**

We also examined the enol ether **310**, where the double bond is not conjugated with the ester group. Compound **310** was prepared according Ley's procedure.[169] In our hands the separation of **310** from its regioisomer **311** and from starting material, β-keto ester **312**, required extensive chromatography.

* Compound **307** is a single isomer whose stereochemistry is as shown, see ref 168



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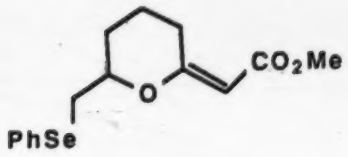

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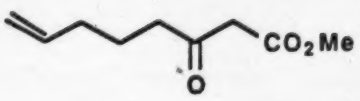
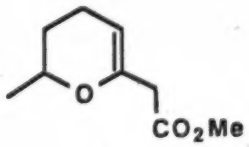


312

When **310** was treated with triphenylstannane under our slow addition conditions, we obtained both **313** and **312** in 70% and 14% yields, respectively. We wondered if, perhaps, the ring opening was due to the presence of tin species in the reaction mixture, but refluxing **310** with $Ph_3SnSePh$ for 12 h did not effect ring opening. It appears, therefore, that β-elimination of enol ether radicals (C-C-O-C=C) does occur but is not a facile process.

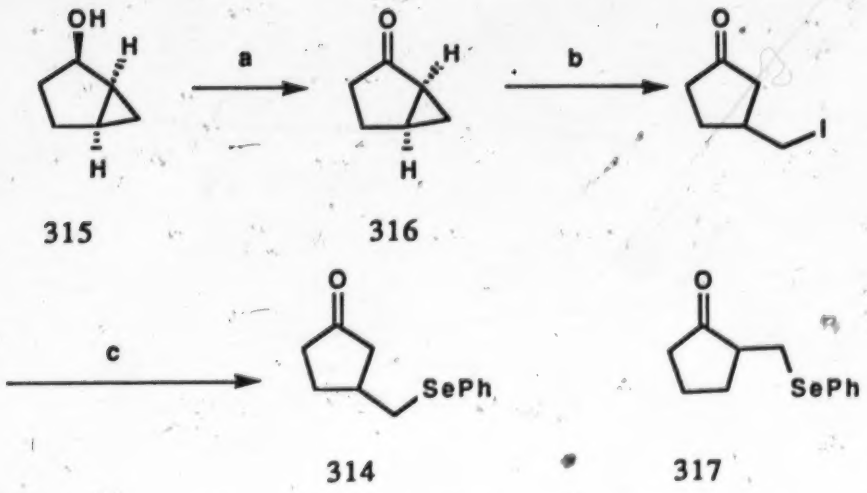


313

All the crude reaction mixtures from the cyclization reactions were analyzed by VPC and only two products were detected (i.e., the cyclized material and the methyl ketone). No products were isolated that arose from oxygen closure.

The formation of **299** and **301** arising from 6-endo closure of the α-keto radical gave rise to the possibility of the intervention of a reversible 5-exo closure. In order to assess the reversibility of the 5-exo cyclization via carbon we prepared **314** from cis-bicyclo[3.1.0]hexan-2-ol according to the following scheme (Scheme 22).

Scheme 22



a) Pyridinium dichromate, 3Å molecular sieves, CH_2Cl_2, room temp., 12 h. b) iodotrimethylsilane, CCl_4, -20°C, 30 min.c) NaSePh, ethanol, 7 h, room temp.

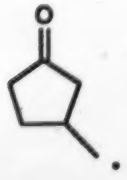
The product **314** was impure even though it was homogeneous by TLC. The identity of the impurity was tentatively determined (IR, ^{13}C, and ^{1}H NMR) as the regioisomer **317** and not 4-(phenylseleno)cyclohexanone.* The amount of impurity was determined as ca. 6%. It was important to determine the identity of the impurity as cyclohexanone is one of the products that would be formed from β-scission of the radical produced from **314** followed by 6-endo closure.

The reaction of **314** with triphenylstannane was performed under our usual slow addition conditions. The majority of the benzene was removed and the yield of 3-methylcyclopentanone was calculated by VPC analysis using authentic 3-

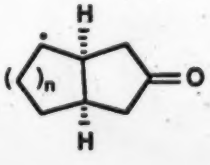
* The authors suggest that the ring opening of **316** is >95% regiospecific, forming 4-iodocyclohexanone as the minor isomer, see ref. 170.

methylcyclopentanone as a calibration standard. The yield was 84%. Careful VPC analysis of the reaction mixture indicated the presence of cyclohexanone (4%) and not 2-methyl cyclopentanone. This observation is in accordance with the original authors observation concerning the regioselectivity of the reaction of **316** with iodotrimethysilane (see foot note on pg. 122).

Therefore, the observed products of 6-endo closure do not arise from an initial and reversible 5-exo ring closure. The radical **318** produced from the selenide **314** should have a greater tendency to undergo β-scission than the radicals **319** for two reasons: i) radical **318** is a primary radical and β-scission would therefore be energetically more favorable than with secondary radicals such as **319** and ii) the radical SOMO of **318** freely rotates and can adopt the optimum conformation for β-scission; the radicals **319** are, perhaps, more conformationally restrained. The formation of the bicyclic compound **299**, resulting from 6-endo closure, is presumably a consequence of the greater conformational flexibility of the seven membered ring versus the five or six membered rings.



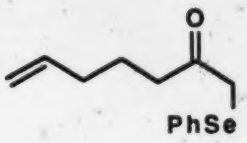
318



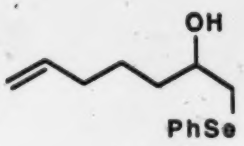
319 n = 1, 2 or 3

We also decided to examine the properties of the 2-oxo-6-hepten-1-yl radical **320** derived from the α-phenylseleno ketone **321**.

320



321



322

Alcohol **322** was prepared in 63% yield by reaction between pent-4-enyl magnesium bromide and (phenylseleno)acetaldehyde according to a procedure method outlined by Petrzilka. Oxidation of **322** using the Corey-Kim oxidant **271** gave **321** in 62% yield.[145]

When **321** was treated with triphenylstannane under our slow addition conditions two major products were formed, cycloheptanone (arising from 7-endo closure) and 3-methylcyclohexanone (arising from 6-exo closure). The yields were determined by VPC analysis using authentic samples for calibration. The yield of cycloheptanone was 41% and of 3-methylcyclohexanone 45%. A small amount (ca. 4%) of reduced material, 6-hepten-2-one * was found. The formation of cis- and trans-5-hepten-2-one, arising form intramolecular 1,5 hydrogen abstraction, was not detected (VPC) (equation 17).

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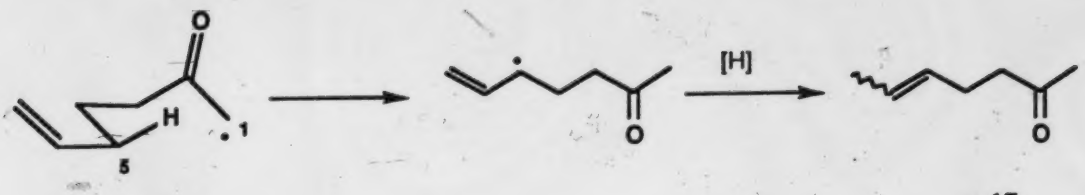
* Prepared by decarboxylation of β-ketoester **308** with 5% aqueous sodium hydroxide (67%).



323 eq 17

The results are quite different from those observed for the 6-heptenyl radical itself. The rate constants for the intramolecular processes of the 6-heptenyl are listed in Table 15.[23,42]

Table 15

6-Hepten-1-yl radical rate constants.

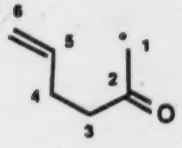
$k_{1,6}$ (exo)	5.4×10^3 (25°C) s^{-1}.
$k_{1,7}$ (endo)	7.5×10^2 (25°C) s^{-1}.
k_{Habs}	5×10^2 (25°C) s^{-1}.

Hydrogen atom abstraction (k_{Habs}) for the 6-heptenyl radical is competitive with endo ring closure, and exo ring closure is an order of magnitude faster that endo ring closure. For the 2-oxo-6-hepten-1-yl radical **323** the endo and exo cyclizations are equally competitive and, apparently, more favored than 1,5 hydrogen atom abstraction.*

It appears that α-keto radicals experience little, if any, kinetic barrier against cyclization via carbon. Their reactivity is certainly different from the analogous carbon radicals. The C1-C2 bond of the α-keto radical **217** is ca 15% olefinic. This will

* It is not possible to say that 1,5 hydrogen atom abstraction is slower than cyclization (exo or endo) for **323** compared with the 6-heptenyl radical, or that cyclization for **323** is faster than 1,5 hydrogen atom abstraction for the 6-heptenyl radical.

impart to the radical a certain amount of rigidity not found in the all carbon analogues. Also the sp^2 center at C-2 will affect the relative disposition of the reactive centers in the transition state for cyclization. Apparently, where possible, 6-endo cyclization occurs and this suggests that approach of the C-1 radical to C-5 is disfavored relative to the approach of C-1 to C-6.* Possibly, this is due to the presence of a small barrier to 5-exo closure of **217** similar to the kinetic barrier against 5-exo closure of the enolate **216.**



217

The fact that the bicyclic selenide **293** cyclizes completely in a 5-exo fashion may well be a consequence of the rigidity of the structure making approach of the radical SOMO to the π^* or π orbital of C-6 relatively difficult. Also the 5-exo cyclization of the norbornenyl radical is extremely fast compared with the 5-hexenyl radical (equation 18).[171]

* This type of explanation has been employed previously to explain the regioselectivity of ring closure of various systems for example see ref. 48.

eq 18

Another conclusion arising from this work is that in the construction of bicyclo[4.3.0.]nonanes and bicyclo[3.3.0]octanes the stereochemical outcome of the ring-fusion is predictable (Table 16).

Table 16

Ring-fusion geometry.

		trans-ring-fusion
n = 1	5-exo-(endo-5)	disfavored
n = 2	5-exo-(endo-6)	disfavored
n = 3	5-exo-(endo-7)	allowed

In summary, our study of α-keto radicals has shown that they can be used to construct bicyclic cyclopentanones and the ring-fusion of the [4.3] and [3.3] systems is always cis.

CONCLUSION

The preceding discussion has shown several examples of radical-based synthetic methodology. In particular the following processes were examined:

(i) a route for converting olefins into α-(phenylmethylene)-γ-lactones.

(ii) a new synthesis of spirolactones.

(iii) a method for converting 2-cyclohexen-1-ylacetic and 2-cyclopenten-1-ylacetic acids, into bicyclic compounds with cis-ring-fusion.

(iv) a route to bicyclic pentanones.

The area of radical cyclization is presently under active development in several laboratories and is likely to occupy an important place in chemical synthesis.

III. EXPERIMENTAL

Unless otherwise stated, the following particulars apply. Experiments were carried out under argon purified by passage through a column (35.x 42 cm) of R 311 catalyst (Chemical Dynamics Corp.) and then dried through a similar column of Drierite.

Glassware was dried in an oven for at least 2 h (155°C), cooled in a desiccator, assembled quickly and sealed with rubber septa (where applicable). Inlet and exit needles were passed through the septa on the apparatus and argon was purged through the system. The exit needle was removed after a few minutes and the apparatus was kept under a slight static pressure of argon (provided no gas was being generated during the reaction). Stirring was effected by using a dry, Teflon coated magnetic stirring bar.

Materials were weighed quickly into dry flasks which were then sealed with rubber septa and purged with argon. Transfer of moisture- and/or air-sensitive reagents was accomplished using dry, well greased syringes whenever possible, solids being dissolved in a suitable solvent prior to transfer. Solvents were distilled for chromatography. Where required, solvents and reagents were dried with suitable drying agents and distilled under argon. Dry ether, tetrahydrofuran and dioxane were distilled from sodium-benzophenone ketyl; benzene and toluene were distilled from sodium; dichloromethane, chloroform, carbon tetrachloride, hexane, pyridine,

triethylamine, diisopropylamine, acetonitrile, dimethylformamide, and isopropylcyclohexylamine were distilled from calcium hydride [the latter two were distilled under reduced pressure (water aspirator with protection from moisture)]. Methanol was distilled from magnesium methoxide; U.S.P. absolute ethanol was used without further drying. Commercial solutions (Aldrich) of methyllithium in ether and n-butyllithium in hexanes were titrated by use of the 2,2-diphenylacetic acid method. Azobis isobutyronitrile (AIBN) was stored at 0°C and used without further purification.

Products were isolated from solution by concentration under water aspirator vacuum at ca. 30°C using a rotatory evaporator. Melting points (uncorrected) were measured using a Kofler block melting point apparatus.

Commercial silica (Merck 60F-254) thin layer chromatography (TLC) plates were used. Silica gel for flash chromatography was Merck type 60 (230-400 mesh). TLC plates were examined under uv radiation (254 nm), treated with iodine vapor or charred on a hot plate after being sprayed with a solution of either i) phosphomolybdic acid (prepared from phosphomolybdic acid (3g, $MoO_3 \cdot 2H_3PO_4 \cdot 48H_2O$) and ceric sulphate [0.5 g, $H_4Ce(SO_4)_4$] in 100 mL of 3% aqueous H_2SO_4. or ii) a solution of o-methoxy benzaldehyde (15 drops) in a 94:6 solution of absolute ethanol:conc H_2SO_4.

Elemental combustion analyses were performed in the microanalytical laboratories of the University of Alberta. Where indicated analyses were recorded on

mixtures of isomers. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer or a Nicolet 7000 FT-IR instrument. Proton NMR were recorded on Bruker WP-80 (at 80 MHz), Bruker WH-200 (at 200 MHz), Bruker WH-300 (at 300 MHz) and Bruker WH-400 (at 400 MHz) instruments. ^{13}C NMR spectra were recorded on the latter 3 machines at 50.3, 75.47 and 100.6 Mhz respectively. All spectra were recorded in deuterated chloroform with tetramethylsilane (TMS) as an internal standard. The following abbreviations are used in the text: s, singlet; d, doublet; t triplet; q, quartet; qu, quintet; se, sextet; h = heptet; m, multiplet; J, coupling constant (±0.25 Hz); δ, chemical shift.

Mass spectra were recorded on an A.E.I. MS 50 mass spectrometer at an ionizing potential of 70 eV. All compounds with asymmetric centers are racemic unless otherwise stated.

In compounds containing the C_6H_5Se group all <u>four</u> resonances in the ^{13}C NMR spectrum were not always observed. The resonances for the carbon atoms of diphenyldiselenide (1M in $CDCl_3$, relative to TMS) are listed below along with the spin lattice relaxation times (T_1 s).[172]

<u>C-1</u> 130.9 (50); <u>o</u>, 131.5 (6.8); <u>m</u>, 129.1 (6.8); <u>p</u>, 127.6 (3.7).

Ethyl 2-butyndioic acid 165:

n-Butyllithium (14.5 mL, 22.5 mmol) was added dropwise over a period of 20 min to a cold (-78°C), stirred solution of ethyl 2-propynoate (2.120 g, 21.6 mmol) in a mixture (20 mL) of THF, diethyl ether and n-pentane (4:4:1). Stirring was continued for a further 10 min and carbon dioxide (dried by passage through a column of Drierite) was bubbled through the solution for 30 min. The mixture was quenched with saturated aqueous ammonium chloride solution (4 mL) and allowed to warm to room temperature. Water (50 mL) and saturated aqueous sodium bicarbonate (20 mL) were then added, the aqueous layer was separated and the organic layer was extracted with saturated aqueous sodium bicarbonate (20 mL). The combined aqueous extracts were acidified to pH 1 with concentrated hydrochloric acid . The aqueous solution was extracted with THF (75 mL) and then with ethyl acetate (2 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Kugelrohr distillation of the residue (100-120 °C, 15 mm) gave acid **165** (2.217 g, 72.2%) as a pale yellow liquid: IR (film) 2985, 1710 (broad) cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 1.58 (t, J = 8.0 Hz, 3H), 4.81 (q, J = 8.0 Hz, 2H), 13.8 (s, 1H); ^{13}C NMR ($CDCl_3$, 15.08 MHz) δ 13.1, 63.1, 93.7, 94.4, 156.3, 157.7; exact mass, m/z 98.0362 (calcd for $C_5H_6O_2$ (M-CO_2)$^{\cdot+}$, m/z 98.0368).

Preparation of Cesium Salts:

Cesium carbonate (anhydrous, Aldrich, 0.5 equiv.) was added slowly to a stirred solution of the acid (approximately 1 g, 1.0 equiv.) in water (5-10 mL). Once gas evolution had ceased the flask was carefully evacuated using an oil pump protected by an 2-propanone dry-ice cold trap and the residual salt dried in vacuo. The salt was used without further purification. Care was taken to exclude moisture while storing the salts as they were moderately deliquescent.

General Procedure for Preparation of β-(Phenylseleno)esters:

The alkene was added dropwise over ca. 5 min to a stirred solution of benzeneselenenyl chloride or benzeneselenenyl bromide in dry acetonitrile at room temperature. After the color of the selenium reagent had been discharged (ca. 1.1 equiv. of alkene, 5 min), the cesium salt, prepared as described above, was added in one portion and the resulting slurry was sonicated overnight at room temperature with protection from light. The mixture was then filtered through a pad of Celite (ca. 3 x 3 cm) using ether for washings and the filtrate was evaporated. Flash chromatography of the residue over silica gel afforded the pure phenylseleno ester as described in individual experiments.

[trans-2-(Phenylseleno)cyclohexyl]-3-phenyl-2-propynoate 159:

The general procedure was followed using benzeneselenenyl bromide (0.8133 g, 3.45 mmol), cyclohexene, acetonitrile (20 mL) and cesium 3-phenyl-2-propynoate (1.067 g, 3.84 mmol). After workup and evaporation of the solvent, flash chromatography of the residue over silica gel (4 x 20 cm) with hexane and then 9:1 hexane-ethyl acetate gave ester **159** (0.9953 g, 75.3%) as a yellow oil: IR (film) 2940, 2222, 1701, 1286 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26-1.82 (bm, 6H), 2.11-2.26 (m, 2H), 3.27 (m, 1H), 5.01 (m, 1H), 7.25-7.32 (m, 2H), 7.25-7.32 (m, 4H), 7.34-7.48 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.4, 25.5, 31.2, 32.2, 45.7, 77.2, 81.0, 86.3, 119.9, 127.7, 128.5, 128.5, 128.9, 130.5, 133.0, 135.4, 153.3; exact mass, m/z 384.0634 (calcd for $C_{21}H_{20}O_2Se$, m/z 384.0628). Anal. Calcd for $C_{21}H_{20}O_2Se$: C, 65.80; H, 5.26; O, 8.35. Found: C, 65.84; H, 5.31; O, 8.31.

[trans-2-(Phenylseleno)cyclohexyl]-2-butynoate 160:

The general procedure was followed using benzeneselenenyl bromide (0.5189 g, 2.20 mmol), cyclohexene, acetonitrile (15 mL) and cesium 2-butynoate (0.5310 g, 2.46 mmol). After workup and evaporation of the solvent, flash chromatography of the residue over silica gel (3 x 20 cm) with hexane and then 94:6 hexane-ethyl acetate gave ester **160** (0.4640 g, 65.7%) as a yellow oil: IR (film) 2940, 2240, 1700, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.80 (bm, 6H), 1.98 (s, 3H), 2.15 (bm,

2H), 3.20 (m, 1H), 4.86 (m, 1H), 7.20-7.40 (m, 3H), 7.55-7.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.8, 23.4, 25.5, 31.2, 32.2, 45.8, 72.8, 76.7, 85.5, 128.3, 127.8, 128.9, 135.6, 153.0; exact mass, m/z 322.0471 (calcd for $C_{16}H_{18}O_2Se$, m/z 322.0472).

Ethyl [trans-2-(phenylseleno)cyclohexyl]-2-butyndioate 161:

The general procedure was followed using benzeneselenenyl bromide (1.124 g, 4.76 mmol), cyclohexene, acetonitrile (20 mL) and cesium 1-ethyl-4-hydrogen-2-butyndioate (1.435 g, 5.24 mmol). After workup and evaporation of the solvent, flash chromatography of the residue over silica gel (3 x 20 cm) with 97:3 hexane-ethyl acetate gave ester **161** (0.495 g, 27.4%) as a yellow oil: IR (film) 1720, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.85 (m, 9H, including t at 1.33, J = 8.0 Hz, 3H), 2.05-2.30 (m, 2H), 3.20 (m, 1H), 4.30 (q, J = 8.0 Hz, 2H), 5.00 (m, 1H), 7.25-7.35 (m, 3H), 7.55-7.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.9, 23.3, 25.3, 31.0, 32.0, 45.3, 62.9, 74.8, 74.9, 78.4, 128.0, 129.1, 135.5, 151.1, 151.8, (1 peak absent from SeC_6H_5); exact mass, m/z 380.0532 (calcd for $C_{18}H_{20}O_4Se$, m/z 380.0527). Anal. Calcd for $C_{18}H_{20}O_4Se$: C, 57.00; H, 5.31. Found: C, 56.79; H, 5.26.

[trans-2-(Phenylseleno)cyclohexyl]-2-propynoate 162:

The general procedure was followed benzeneselenenyl chloride (0.4208 g, 2.20 mmol), cyclohexene, acetonitrile (10 mL) and cesium 2-propynoate (0.667 g, 3.30 mmol). After workup and evaporation of the solvent, flash chromatography of the residue over silica gel (3 x 15 cm) with 19:1 hexane-ethyl acetate gave ester **162** (0.5400 g, 80.0%) as a yellow oil: IR (film) 1711, 1332 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.15-1.80 (m, 6H), 2.05-2.30 (m, 2H), 2.88 (s, 1H), 3.20 (m, 1H), 4.95 (m, 1H), 7.20-7.40 (m, 3H), 7.55-7.70 (m, 2H); exact mass, m/z 308.0312 (calcd for $C_{15}H_{16}O_2Se$, m/z 308.0315). Anal. Calcd for $C_{15}H_{16}O_2Se$: C, 58.64; H, 5.25; O, 10.41. Found: C, 58.66; H, 5.17; O, 10.33.

[trans-2-(Phenylseleno)cyclopentyl]-3-phenyl-2-propynoate 163:

The general procedure was followed using benzeneselenenyl bromide (0.5734 g, 2.43 mmol), cyclopentene, acetonitrile (15 mL) and cesium 3-phenyl-2-propynoate (0.746 g, 2.68 mmol). After workup and evaporation of the solvent, flash chromatography of the residue over silica gel (3 x 20 cm) with 96:4 hexane-ethyl acetate gave ester **163** (0.7163 g, 79.8%) as a yellow oil: IR (film) 2965, 2220, 1700, 1280, 1190, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.64-1.94 (m, 4H), 2.12-2.40 (m, 2H), 3.74 (m, 1H), 5.30 (m, 1H), 7.16-7.52 (m, 6H), 7.54-7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 22.7, 30.8, 31.0, 31.2, 45.7, 83.4, 86.3, 119.6,

127.7, 128.2, 128.6, 129.1, 130.6, 132.9, 134.3, 153.3; exact mass, m/z 370.0471 (calcd for $C_{20}H_{18}O_2Se$, m/z 370.0472). Anal. Calcd for $C_{20}H_{18}O_2Se$: C, 65.04; H, 4.91; O, 8.66. Found: C, 65.31; H, 4.84; O, 8.82.

[trans-2-(Phenylseleno)cycloheptyl]-3-phenyl-2-propynoate 164:

The general procedure was followed using phenylselenenyl bromide (0.5847 g, 2.48 mmol), cycloheptene, acetonitrile (10 mL) and cesium 3-phenyl-2-propynoate (0.7565 g, 2.72 mmol). After workup and evaporation of the solvent, flash chromatography of the residue over silica gel (3 x 20 cm) with 96:4 hexane-ethyl acetate gave ester **164** (0.6630 g, 67.3%) as a yellow oil: IR (film) 2930, 1705, 1285, 1195, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.40-2.00 (bm, 9H), 2.12-2.32 (m, 1H), 3.52 (m, 1H), 5.28 (m, 1H), 7.24-7.52 (m, 6H), 7.54-7.72 (m, 4H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 21.9, 26.4, 28.1, 31.4, 31.8, 48.2, 80.0, 86.0, 119.7, 127.7, 128.4, 128.9, 130.4, 132.9, 135.0, 153.1, (1 peak absent from SeC_6H_5); exact mass, m/z 398.0788 (calcd for $C_{22}H_{22}O_2Se$, m/z 398.0785). Anal. Calcd for $C_{22}H_{22}O_2Se$: C, 66.50; H, 5.58; O, 8.05. Found: C, 66.60; H, 5.51; O, 8.03.

General Procedure for Radical Cyclization:

A flask containing the substrate and a Teflon-coated magnetic stirring bar was equipped with a reflux condenser fitted with a rubber septum. The apparatus was

purged with argon and anhydrous benzene was then added by syringe. The mixture was then refluxed in an oil bath. Benzene solutions of the tin hydride and azoisobutyronitrile (AIBN, Eastman) were added over a number of hours using a double syringe pump. Refluxing was continued for a further specified period. The solvent was evaporated and flash chromatography of the residue over silica gel yielded the pure product as described in individual experiments. For a discussion of this technique see the footnote on page 58.

(E)-(3aα,6aα)-Hexahydro-3-(phenylmethylene)-2H-cyclopenta[b]furan-2-one 166: *

The general procedure was followed using **163** (0.2078 g, 0.563 mmol) in benzene (20 mL), triphenylstannane (0.20 mL, 0.784 mmol) in benzene (10 mL), AIBN (0.0150 g, 0.091 mmol) in benzene (10 mL) and an addition period of ca. 8 h. After a further 8 h the benzene was evaporated and flash chromatography of the residue over silica gel (2 x 15 cm) with 88:12 hexane-ethyl acetate yielded lactone **166** (0.0890 g, 73.8%) as a colorless oil: IR (film) 2961, 1752, 1187 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.50-2.20 (bm, 6H), 3.85 (m, 1H), 5.05 (m, 1H), 7.35-7.65 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.7, 32.0, 33.3, 42.2, 83.5, 129.4, 130.4, 131.0, 134.9, 137.1, 173.8 (resonance for olefinic carbon absent); exact mass, m/z 214.0994 (calcd for $C_{14}H_{14}O_2$, m/z 214.0994). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H,

6.59. Found: C, 78.57; H, 6.64.

* (E) Stereochemistry tentatively assigned.

(E)-(3aα,7aα)-Hexahydro-3-(phenylmethylene)-2H-benzofuran-2-one

(E)-(3aα,7aβ)-Hexahydro-3-(phenylmethylene)-2H-benzofuran-2-one

167: *

The general procedure was followed using **159** (0.1482 g, 0.387 mmol) in benzene (20 mL), triphenylstannane (0.14 mL, 0.549 mmol) in benzene (10 mL), AIBN (0.0140 g, 0.085 mmol) in benzene (10 mL) and an addition period of ca. 8 h. After a further 8 h the benzene was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm) with 9:1 hexane-ethyl acetate yielded lactone **167** (0.0640 g, 72.4%) as a TLC pure colorless oil: IR (film) 2952, 1760, 1192, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) (data for two isomers) δ 1.2-1.8 (bm, 6H), 2.0-2.4 (m, 2H), 3.35 (m, 1H), 4.50 (m, 1H), 7.3-7.8 (m, 6H), with minor peaks at 2.70 (m) and 3.75 (m) (corresponding to the trans isomer); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 19.0, 22.8, 25.8, 26.8, 38.3, 75.5, 127.5, 128.0, 128.8, 132.5, 134.1, 134.4, 171.5; exact mass (isomer mixture), m/z 228.1149 (calcd for $C_{15}H_{16}O_2$, m/z 228.1150). Anal. (Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found (isomer mixture): C, 78.99; H, 6.96.

* (E) Stereochemistry tentatively assigned.

(E)-(3aα,8aα)-octahydro-3-(phenylmethylene)-2H-cyclohepta[b]furan-2-one, (E)-(3aβ,8aβ)-octahydro-3-(phenylmethylene)-2H-cyclohepta[b]furan-2-one 168 : *

The general procedure was followed using **164** (0.1600 g, 0.403 mmol) in benzene (20 mL), triphenylstannane (0.14 mL, 0.549 mmol) in benzene (10 mL), AIBN (0.0150 g, 0.091 mmol) in benzene (10 mL) and an addition period of ca. 8 h. After a further 8 h the benzene was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm) with 89:11 hexane-ethyl acetate yielded lactones **168** (0.0678 g, 69.4%) as a TLC pure colorless oil: IR (film) 2920, 1746, 1189, 1177 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) (data for both isomers) δ 1.10-1.90 (bm, 17H), 1.35 (m, 3H), 3.30 (m, 1H), 3.60 (m, 1H), 4.20 (m, 1H), 4.70 (m, 1H), 7.3-7.75 (m, 12H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) (data for both isomers) δ 22.8, 24.9, 25.3, 26.9, 27.4, 27.6, 29.2, 30.7, 31.4, 32.9, 43.9, 44.6, 81.0, 83.3, 128.5, 129.0, 129.2, 129.6, 129.7, 130.1, 131.3, 131.5, 134.3, 134.4, 136.3, 137.4, 171.0, (only 1 C=O resonance observed); exact mass (isomer mixture), m/z 242.1303 (calcd for $C_{16}H_{18}O_2$, m/z 242.1307). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found (isomer mixture): C, 79.06; H, 7.32.

* (E) Stereochemistry tentatively assigned.

(E)-(1-chlorocyclohexyl)methyl 2-butenoate 175b:

Sodium borohydride (0.400 g, 10.6 mmol) was added at room temperature to a stirred solution of **176b** (1.044 g, 85% pure by GLC, 6.05 mmol) in absolute ethanol (20 mL). After 30 min water (5 mL) was added and the ethanol was evaporated. A further portion (10 mL) of water was added and the mixture was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to yield the crude alcohol **177b** (0.9356g). The crude material contained no aldehyde [^{1}H NMR (80 MHz)]. 4-N,N-Dimethylaminopyridine (0.080 g, 0.7 mmol) was added to a stirred solution of the crude alcohol and trans-2-butenoic anhydride (1.1 mL, 7.0 mmol) in pyridine (10 mL) at room temperature. The solution was stirred for 3 h and then poured into a mixture of concentrated hydrochloric acid (10 g) and ice (150 g). The solution was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were washed with saturated sodium bicarbonate (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm) with 96:4 hexane-ethyl acetate yielded ester **175b** (0.681 g, 51.9%) as a clear colorless liquid: IR (film) 2930, 1710, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18-1.30 (m, 1H), 1.58-1.86 (bm, 7H), 1.90-1.98 (m, 5H including dd at 1.90 J = 7, 2 Hz), 4.24 (s, 2H), 5.92 (dq, J = 15.5, 2 Hz, 1H), 7.04 (dq, J = 15.5, 7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 17.9, 21.5, 25.2, 36.2, 71.5, 71.7, 122.2, 145.2, 165.8; exact mass, m/z 181.1224 [calcd for $(M-Cl)^+$ $C_{11}H_{17}O_2$, m/z 181.1228]. Anal.

Cald for $C_{11}H_{17}ClO_2$: C, 60.97; H, 7.91; Cl, 16.36 Found, C, 60.29; H, 7.78; Cl, 17.44.

(E)-(1-Nitrocyclohexyl)methyl 2-butenoate 175c:

4-N,N-Dimethylaminopyridine (0.040 g, 0.33 mmol) was added to a stirred solution of **177c** (0.5896 g, 3.70 mmol) and trans-2-butenoic anhydride (0.60 mL, 4.0 mmol) in pyridine (5 mL) at room temperature. The solution was stirred for a further 2 h and then poured into a mixture of concentrated hydrochloric acid (5.5 g) and ice (150 g). The solution was extracted with diethyl ether (2 x 50 mL) and the combined organic extracts were washed with brine (25 mL) and dried ($MgSO_4$). Evaporation of the solvent and Kugelrohr distillation of the residue (bp 130°C, 3 mm) yielded the ester **175c** (0.6385 g, 75.9%) as a clear liquid: IR (film) 2940, 1720, 1540, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36-1.68 (bm, 6H), 1.70-1.82 (m, 2H), 1.90 (dd, J = 7.0, 1.5 Hz, 3H), 2.34-2.44 (m, 2H), 4.44 (s, 2H), 5.82 (dq, J = 15.5, 1.5 Hz, 1H), 6.98 (dq, J = 15.5, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz, ORD) (multiplicity) δ 18.0 (q), 21.9 (m), 22.3 (m), 24.7 (t), 31.3 (t), 89.7 (s), 121.6 (d), 146.2 (d), 165.3 (s); exact mass, m/z 181.1226 (calcd for $C_{11}H_{17}O_2$, m/z 181.1228, $(M-NO_2)^+$). Anal. Cald for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16 Found, C, 57.98; H, 7.52; N, 6.01.

[1-(Phenylseleno)cyclohexyl]methyl 3-butenoate 187:

Trans-2-butenoyl chloride (0.35 mL, 3.7 mmol) was added to a stirred solution of alcohol **172** (0.9176 g, 3.41 mmol), triethylamine (0.50 mL, 3.6 mmol) and N,N-dimethyl-4-aminopyridine (0.030 g, 0.25 mmol) in dichloromethane (20 mL). The solution was refluxed for 22 h and then allowed to cool to room temperature. The solution was washed with saturated sodium hydrogen carbonate (10 mL), dilute hydrochloric acid (10 mL, 1M) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm) with 96:4 hexane-ethyl acetate yielded **187** (0.8624 g, 75.0%) as a yellow oil: IR (film) 2930, 1735, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.16-1.96 (bm, 10 H), 3.10 (dt, J = 7, 1.4 Hz, 2H), 4.14 (s, 2H), 5.16 (m, 1H), 5.22 (m, 1H), 5.96 (ddt, J = 17.5, 10, 7 Hz, 1H), 7.24-7.44 (m, 3H), 7.50-7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 22.3, 25.7, 33.0, 39.1, 51.8, 71.3, 118.5, 122.5, 126.4, 128.8, 130.3, 138.4, 171.2; exact mass, m/z 338.0778 (calcd for $C_{17}H_{22}O_2Se$, m/z 338.0785). Anal. Calcd for $C_{17}H_{22}O_2Se$: C, 60.53; H, 6.57; O, 9.49. Found: C, 60.73; H, 6.52; O 9.29.

Preparation of bis(Phenylseleno)cycloalkanes:

1,1-bis(Phenylseleno)cyclopentane 188:

Cyclopentanone (2.10 mL, 24.0 mmol) was added dropwise over ca. 20 min to

a stirred solution of benzeneselenol (7.46 g, 47.5 mmol) and anhydrous zinc chloride (1.69 g, 12.4 mmol) in carbon tetrachloride (100 mL) at room temperature. After being stirred for 3.5 h the reaction mixture was added to 5% aqueous hydrochloric acid (50 mL). The organic layer was separated, washed with saturated sodium hydrogen carbonate (50 mL) and water (20 mL), dried ($MgSO_4$) and evaporated. The residue was dissolved in a solution of benzene (10 mL) and methanol (10 mL) and then sodium borohydride was added until the yellow color was discharged. The solution was immediately partitioned between n-pentane (200 mL) and 5% aqueous sodium hydrogen carbonate (60 mL). The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was dissolved in the minimum amount of hot hexane and cooled to 0°C. The precipitate was removed by filtration, washed with cold (0°C) n-pentane and dried under high vacuum (0.1 mm) for 5 h to yield **188** (4.97 g, 54.5%) as white platelets: mp 75°C (lit[173]. mp 73-75°C), IR (hexane cast) 2950, 1474, 743, 691 cm^{-1}; exact mass, m/z 382.9781 (calcd for $C_{17}H_{18}Se_2$, m/z 382.9817).

1,1-bis(Phenylseleno)cycloheptane 190:

The procedure employed for **188** was followed using cycloheptanone (2.80 mL, 23.7 mmol), benzeneselenol (7.53 g, 48.0 mmol) and zinc chloride (1.63 g, 12.0 mmol) in carbon tetrachloride (75 mL). Workup and purification yielded **190** (4.68 g,48.4%) as a white solid: mp 67-67.5°C: IR (hexane cast) 2920, 1430, 690 cm^{-1}; ^1H

NMR ($CDCl_3$, 200 MHz) δ 1.5 (bs, 8H), 2.14 (m, 4H), 7.24-7.46 (m, 6H), 7.66-7.78 (m, 4H); exact mass, m/z 410.0049 (calcd for $C_{19}H_{22}Se_2$, m/z 410.0052). Anal. Calcd for $C_{19}H_{22}Se_2$: C, 55.89; H, 5.43. Found: C, 55.62; H, 5.46.

1,1-bis(Phenylseleno)cyclohexane 189:

Concentrated sulphuric acid (3.75 mL, 70.4 mmol) was added dropwise to a stirred solution of cyclohexanone (5.00 mL, 48.2 mmol) and bezeneselenol (15.79 g, 101 mmol) in carbon tetrachloride (50 mL) at -5°C. Argon was bubbled through this solution throughout the experiment. After 15 min at -5°C the cooling bath was removed and stirring was continued for a further 30 min. The reaction mixture was then poured cautiously into a solution of potassium carbonate (8.0 g, 58 mmol) in water (150 mL). The resulting mixture was diluted with diethyl ether (250 mL), washed with saturated sodium hydrogen carbonate (2 x 50 mL), dried ($MgSO_4$) and evaporated. The residue was dissolved in a solution of benzene (20 mL) and methanol (20 mL) and sodium borohydride was added until the yellow color was discharged. The solution was then immediately partitioned between hexane (200 mL) and 5% sodium hydrogen carbonate (100 mL) and the organic layer was dried ($MgSO_4$), and evaporated. The residue was washed with cold hexane and dried overnight under in vacuo (0.1 mm) to yield **189** (11.9 g, 62.6%) as a white solid: mp 80-82°C; IR (hexane cast) 2920, 743, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.36 (m,

2H), 1.52-1.70 (m, 4H), 1.80-1.90 (m, 4H), 7.24-7.42 (m, 6H), 7.66-7.78 (m, 4H); exact mass, m/z 239.0337 [calcd for $C_{12}H_{15}Se$ (M-SeC_6H_5)$^+$, m/z 239.0339]. Anal. Calcd for $C_{18}H_{20}Se_2$: C, 54.83; H, 5.11. Found: C, 54.92; H, 5.13.

1,1-bis(Phenylseleno)cyclooctane 193:

The procedure employed for **189** was followed using concentrated sulphuric acid (3.5 mL, 65.7 mmol), cyclooctanone (6.23 g, 49.4 mmol) and benzeneselenol (15.67 g, 99.8 mmol) in carbon tetrachloride (50 mL). After workup and removal of the diphenyldiselenide the residue was washed with cold hexane to yield **193** (7.98 g, 38.3%) as white platelets: mp 83-84°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.4-1.76 (bm, 10H), 1.95-2.05 (m, 4H), 7.16-7.40 (m, 6H), 7.60-7.76 (m, 4H); exact mass, m/z 267.0643 [calcd for $C_{14}H_{19}Se$ (m-SeC_6H_5), m/z 267.0652]. Anal. Calcd for $C_{20}H_{24}Se_2$: C, 56.88; H, 5.73. Found: C, 56.75; H, 5.66.

1,1-bis(Phenylseleno)-4-tert-butyl-cyclohexane 184:

Concentrated sulphuric acid (1.7 mL, 31.9 mmol) was added dropwise to a stirred solution of 4-tert-butylcyclohexanone (2.742 g, 17.8 mmol) and benzeneselenol (3.6 mL, 34 mmol) in carbon tetrachloride (30 mL) at 0°C. Argon was bubbled through the solution throughout the experiment. After 45 min the cooling bath was removed and stirring was continued for a further 30 min. Sodium carbonate (6.8 g, 64

mmol) was cautiously added to the reaction mixture followed by water (10 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (20 mL). The organic layers were combined, washed with saturated sodium hydrogen carbonate (15 mL), dried (Na_2SO_4) and evaporated. The residue was dissolved in a solution of benzene (10 mL) and methanol (10 mL) and sodium borohydride was added until the yellow color was discharged. The solution was then immediately partitioned between n-pentane (200 mL) and 5% sodium hydrogen carbonate (100 mL) and the organic layer was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm) with hexane (1.5 L) and 98:2 hexane-ethyl acetate yielded **184** (4.9761 g, 62.1%) as a white solid: mp 89-91°C (lit[173]. mp 89-91°C); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.84 (bs, 11H), 1.36-1.88 (bm, 6H), 2.00-2.16 (m, 1H), 7.24-7.26 (m, 6H), 7.60-7.68 (m, 2H), 7.80-7.88 (m, 2H); exact mass, m/z 295.0951 [calcd for $C_{16}H_{23}Se$ $(M\text{-}SeC_6H_5)^+$, m/z 295.0965].

General procedure for the preparation of 1-(phenylseleno) cycloalkycarbaldehydes:

n-Butyllithium (1.05 equiv.) was added dropwise over 5-10 min to a stirred solution of the bis(phenylseleno)acetal in THF at -78°C. After 5 min N,N-dimethylformamide (DMF) (1.3-1.5 equiv.) was added rapidly and the mixture was stirred for 5 min and then quenched at -78°C with either saturated aqueous ammonium

chloride or brine. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The organic layers were combined, dried ($MgSO_4$) and evaporated The product was purified as described for individual experiments.

1-(Phenylseleno)cyclohexanecarbaldehyde 171: [90]

The general procedure was followed using **189** (5.254 g, 13.3 mmol) in THF (150 mL), n-butyllithium (9.2 mL, 1.55 M in hexanes, 14.2 mmol), and DMF (1.60 mL, 20.7 mmol). After workup flash chromatography of the residue over silica gel (5 x 20 cm) with 99:1 and then 98:2 hexane-ethyl acetate yielded aldehyde **171** (3.187 g, 89.7%) as a yellow oil: IR (film) 2932, 1705, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.24-2.00 (bm, 10H), 7.22-7.54 (m, 5H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 24.0, 25.5, 30.8, 59.7, 125.1, 129.0, 129.4, 137.8, 192.6; exact mass, m/z 268.0361 (calcd for $C_{13}H_{16}OSe$, m/z 268.0366).

1-(Phenylseleno)cyclopentanecarbaldehyde 181:

The general procedure was followed using **188** (4.965 g, 13.1 mmol), n-butyllithium (9.2 mL, 1.5 M in hexanes, 13.8 mmol), and DMF (1.50 mL, 19.4 mmol) in THF (100 mL). After workup flash chromatography of the residue over silica gel (5 x 20 cm) with 99:1 and then 96:4 hexane-ethyl acetate yielded the aldehyde **181** (2.794 g, 84.2%) as a yellow oil: IR (film) 2960, 1700, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 200

MHz) δ 1.52-2.20 (bm, 8H), 7.22-7.58 (m, 5H), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.7, 32.3, 63.0, 127.1, 129.1, 136.8, 193.4, (1 peak absent from SeC_6H_5); exact mass, m/z 254.0212 (calcd for $C_{12}H_{14}OSe$, m/z 254.0210). Anal. Calcd for $C_{12}H_{14}OSe$: C, 56.92; H, 5.41; O, 6.32. Found: C, 57.02; H, 5.58; O, 6.49.

2-(Cycloheptylseleno)benzaldehyde 192 and 1-(phenylseleno) cycloheptanecarbaldehyde 191:

The general procedure was followed using **190** (4.6750 g, 11.45 mmol), n-butyllithium (8.0mL, 1.45 M in hexanes, 11.6 mmol), and DMF (2.70 mL, 34.9 mmol) in THF (125 mL). After workup flash chromatography of the residue over silica gel (5cm x 20 cm) with 97:3 hexane-ethyl acetate yielded **192** and **191** [2.389 g, 49:51 (^1H NMR 200 MHz), 74.2% (combined yield)] as a yellow oil. In a previous experiment **192** and **191** were separated by centrifugal chromatography (Chromatotron, 2mm plate, Merck silica gel 60 PF_{254}) with 99:1 hexane-ethyl acetate **192** had IR (film) 2925, 1693, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.38-1.88 (bm, 10H), 2.02-2.22 (m, 2H), 3.40-3.56 (m, 1H), 7.32-7.54 (m, 2H), 7.58-7.66 (m, 1H), 7.84-7.90 (m, 1H), 10.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.32 ~~MHz)~~ δ 26.8, 28.1, 35.1, 44.2, 126.7, 131.9, 133.7, 133.8, 193.3; exact mass, m/z 282.0528 (calcd for $C_{14}H_{18}OSe$, m/z 282.0523). **191** had: IR (film) 2925, 1707, 741 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26-2.12 (bm, 12H), 7.24-7.52 (m, 5H), 9.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 23.8, 24.5, 32.6, 63.3, 129.1, 129.5, 137.9, 193.2, (1 peak absent from SeC_6H_5); exact mass, m/z 282.0527 (calcd for $C_{14}H_{18}OSe$, m/z 282.0523).

4-tert-Butyl-1-(phenylseleno)cyclohexanecarbaldehyde 183: [97]

The general procedure was followed using **184** (4.911 g, 10.9 mmol) in THF (75 mL), n-butyllithium (8.6 mL, 1.3 M in hexanes, 11.4 mmol), and DMF (1.05 mL, 13.6 mmol). After workup flash chromatography of the residue over silica gel (5 x 20 cm) with 99:1 then 96:4 hexane-ethyl acetate yielded aldehyde **183** (2.850 g, 80.9%) as a yellow oil: IR (Nujol) 2920, 1705, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.72-0.98 (m, 11H, including s at 0.77, 9H), 1.02-1.10 (m, 1H), 1.70-1.80 (m, 4H), 2.08-2.11 (m, 2H), 7.24-7.30 (m, 2H), 7.34-7.40 (m, 1H), 7.44-7.50 (m, 2H), 9.14 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.1, 27.4, 32.1, 32.3, 47.4, 58.6, 125.1, 128.9, 129.4, 137.8, 192.6; exact mass, m/z 324.0990 (calcd for $C_{17}H_{24}OSe$, m/z 324.0992).

General Procedure for the Preparation of β-Hydroxy Phenylselenides.

Borane-dimethyl sulfide complex [3 equiv., 2 M in toluene, (Aldrich)] was added dropwise at room temperature over 30 to 50 min to a stirred solution of the

aldehyde in dichloromethane. After ca. 2 h (followed by TLC in each individual case) the reaction was quenched by pouring the solution into a mixture of saturated ammonium chloride and water (2:1). When the evolution of hydrogen had subsided, the organic layer was separated and the aqueous layer was extracted with diethyl ether. The organic extracts were combined, dried ($MgSO_4$) and evaporated. The crude alcohol was purified further as described for individual experiments.

[1-(Phenylseleno)cyclohexyl]methanol 172:

The general procedure was followed using aldehyde **171** (2.8694 g, 10.74 mmol) and borane-dimethyl sulfide complex (16.0 mL, 2 M in toluene, 32.0 mmol) in dichloromethane (100 mL). After workup, flash chromatography of the residue over silica gel (5 x 20 cm) with 90:10 hexane-ethyl acetate yielded alcohol **173** (2.1851 g, 75.6%) as a yellow oil: IR (film) 3440, 2930, 1020, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26-1.86 (bm, 10 H), 2.5 (t, J = 6.5 Hz, 1H), 3.28 (d, J = 6.5 Hz, 2H), 7.26-7.42 (m, 3H), 7.56-7.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.5, 26.2, 33.3, 58.9, 68.2, 125.8, 128.9, 129.0, 138.1; exact mass, m/z 270.0518 (calcd for $C_{13}H_{18}OSe$, m/z 270.0523). Anal. Calcd for $C_{13}H_{18}OSe$: C, 57.99; H, 6.74; O, 5.94. Found: C, 58.21; H, 6.72; O, 6.00.

[1-(Phenylseleno)cyclopentyl]methanol 198:

The general procedure was followed using aldehyde **181** (1.7685 g, 6.984 mmol) and borane-dimethyl sulfide complex (10.5 mL 2M in toluene, 21 mmol) in dichloromethane (100 mL). After workup, flash chromatography of the residue over silica gel (5 x 20 cm) with 90:10 (1.5 L) and then 87.5:12.5 (2.0 L) hexane-ethyl acetate yielded alcohol **198** (1.5693 g, 88.0%) as a yellow oil: IR (film) 3420, 2950, 1020, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.54-1.98 (bm, 8H), 1.52 (t, J = 6.5 Hz, 1H), 3.34 (d, J = 6.5 Hz, 2H), 7.27-7.46 (m, 3H), 7.58-7.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 24.5, 63.0, 62.9, 67.6, 127.5, 128.7, 128.9, 137.4; exact mass, m/z 256.0364 (calcd for $C_{12}H_{16}OSe$, m/z 256.0366). Anal. Calcd for $C_{12}H_{16}OSe$: C, 56.48; H, 6.32; O, 6.27. Found: C, 56.59; H, 6.33; O, 6.12.

[1-(Phenylseleno)cycloheptyl]methanol 200 and o-(cycloheptylseleno) benzyl alcohol 201:

The general procedure was followed using aldehyde **191** [1.207 g, as a mixture with **192**, 51% **191** (^1H NMR 200 MHz), 4.29 mmol] and borane-dimethyl sulfide complex (6.5 mL, 2 M in toluene, 13.0 mmol) in dichloromethane (75 mL). After workup centrifugal chromatography (Chromatotron, 4 mm plate, Merck silica gel 60 PF_{254}) with 96:4 hexane-ethyl acetate yielded alcohol **200** (0.3579 g, 29.5%) and **201** (0.4054 g, 33.4%) as yellow oils: **200** had IR (film) 3360, 2926, 1028, 751 cm^{-}

1; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.38-1.82 (bm, 12H), 1.54 (t, J = 6.5 Hz, 1H), 3.16 (d, J = 6.5 Hz, 2H), 7.26-7.44 (m, 3H), 7.52-7.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 23.4, 30.5, 35.6, 66.9, 76.1, 119.1, 129.0, 138.1, (1 peak absent from SeC_6H_5); exact mass, m/z 284.0687 (calcd for $C_{14}H_{20}OSe$, m/z 284.0679). Anal. Calcd for $C_{14}H_{20}OSe$: C, 59.36; H, 7.12; O, 5.65. Found: C, 59.53; H, 7.06; O, 5.32. **201** had: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.2-1.8 (bm, 10H), 1.96-2.14 (bm, 2H), 2.42 (t, J = 6.5 Hz, 1H), 3.46 (hep, J = 4 Hz, 1H), 4.76 (d, J = 6.5 Hz, 2H), 7.16-7.34 (bm, 2H), 7.40 (m, 1H), 7.58 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.7, 28.1, 35.6, 45.7, 65.7, 127.9, 128.2, 128.5, 130.1, 135.6, 143.3; exact mass, m/z 284.0676 (calcd for $C_{14}H_{20}OSe$, m/z 284.0679). Anal. Calcd for $C_{14}H_{20}OSe$: C, 59.36; H, 7.12; O, 5.65. Found: C, 59.19; H, 7.13; O, 5.37.

[4-tert-Butyl-1-(phenylseleno)cyclohexyl]methanol 206:

The general procedure was followed using aldehyde **183** (1.3695 g, 4.24 mmol) and borane-dimethyl sulfide complex (6.0 mL, 2 M in toluene, 12.0 mmol) in dichloromethane (50 mL). After workup flash chromatography of the residue over silica gel (5 x 20 cm) with 90:10 hexane-ethyl acetate yielded alcohol **206** (1.0582 g, 76.7%) as a pale yellow solid: IR (film) 3460, 2940, 1055, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.84 (s, 9H), 1.00-1.30 (bm, 3H), 1.50-2.06 (bm, 6H), 2.42 (bs, 1H), 3.42 (bs, 2H), 7.26-7.46 (m, 3H), 7.56-7.66 (m, 2H); ^{13}C NMR ($CDCl_3$,

100.6 MHz) δ 24.0, 27.5, 32.5, 34.8, 47.6, 56.8, 62.6, 125.7, 128.8, 138.2, (1 peak absent from SeC_6H_5); exact mass, m/z 326.1158 (calcd for $C_{17}H_{26}OSe$, m/z 326.1149). Anal. Calcd for $C_{17}H_{26}OSe$: C, 62.76; H, 8.05; O, 4.92. Found: C, 63.06; H, 8.13; O, 5.05.

[1-(Phenylseleno)cyclooctanyl]carbaldehyde 194 and [1-(phenylseleno)cyclooctyl]methanol 203.

The general procedure (see p. 147) was followed using **193** (1.5915 g, 3.78 mmol), n-butyllithium (2.6 mL, 1.55 M in hexanes, 4.0 mmol) and DMF (0.9 mL, 11.6 mmol) in THF (75 mL). After workup flash chromatography of the residue over silica gel (2 x 20 cm) with 97:3 hexane-ethyl acetate yielded **194** [0.5803 g, as a mixture with **195**, 51.6% (combined yield)] as a yellow oil. The aldehydes were used in the following experiment without further purification.

The general procedure was followed using aldehyde **194** (0.4845 g, as a mixture with **195**, 1.64 mmol) and borane-dimethyl sulfide complex (1.6 mL, 2 M in toluene, 3.2 mmol) in dichloromethane (25 mL). After workup flash chromatography of the residue over silica gel (5 x 20 cm) with 95:5 hexane-ethyl acetate followed by centrifugal chromatography (Chromatotron, 2 mm plate, Merck silica gel 60 PF_{254}) yielded **203** (0.2597 g, 53.2%) and **204** (0.1555 g, 31.9%) as yellow oils: **203** had IR (CH_2Cl_2 cast) 3656, 2920, 1052, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.40-

1.84 (bm, 14 H), 2.56 (t, J = 6Hz, 1H), 3.22 (d, J = 6Hz, 2H), 7.24-7.46 (m, 3H), 7.52-7.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 23.4, 25.4, 28.5, 30.4, 63.5, 65.9, 126.5, 128.9, 129.0, 138.1; exact mass, m/z 298.0840 (calcd for $C_{15}H_{22}OSe$, m/z 298.0836). Anal. Calcd for $C_{15}H_{22}OSe$: C, 60.60; H, 7.46; O, 5.38. Found: C, 60.89; H, 7.52; O, 5.15.

General Procedure for the preparation of Butenoates:

n-Butyllithium (1.5 equiv.) was added to a stirred solution of the β-hydroxyselenide and 2,2'-dipyridyl (0.5 mg) in dry THF at -78°C, until the indicator turned red. Then a further portion was added equal to half of the volume already injected. After 10 min trans-2-butenoyl chloride (3 equiv.) was added rapidly in one portion. The reaction was quenched after 1 h at - 78°C with saturated ammonium chloride (2 mL). The ice bath was removed and the mixture was allowed to warm rapidly to room temperature. Brine (10 mL) was added, the organic layer was separated and the aqueous layer extracted with diethyl ether (25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified further as described for the individual experiments.

(E)-[1-(Phenylseleno)cyclohexyl]methyl 2-butenoate 173:

The general procedure was followed using alcohol 172 (0.6140 g, 2.28 mmol)

in THF (20 mL), n-butyllithium (2.3 mL, 1.5 M in hexanes, 3.45 mmol) and trans-2-butenoyl chloride (0.65 mL, 6.8 mmol). After workup flash chromatography of the residue over silica gel (3 x 15 cm) with 96.5:3.5 hexane-ethyl acetate gave ester 173 (0.576 g, 74.9%) as a yellow oil: IR (film) 2920, 1705, 1185 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.14-1.90 (bm, 13 H; including dd at 1.86, J = 7.0, 2.0 Hz, 3H), 4.12 (s, 2H), 5.82 (dq, J = 15.0, 2.0 Hz, 1H), 6.96 (dq, J = 15.0, 7.0 Hz, 1H), 7.22-7.40 (m, 3H), 7.58-7.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 18.0, 22.5, 25.8, 33.2, 52.1, 70.8, 122.7, 126.5, 128.8, 128.8, 138.4, 144.7, 166.3; exact mass, m/z 383.0786 (calcd for $C_{17}H_{22}O_2Se$, m/z 338.0785). Anal. Calcd for $C_{17}H_{22}O_2Se$: C, 60.53; H, 6.57; O, 9.49. Found: C, 60.46; H, 6.59; O, 9.75.

(E)-[1-(Phenylseleno)cyclopentyl]methyl 2-butenoate 199:

The general procedure was followed using alcohol 198 (0.5352 g, 2.10 mmol) in THF (20 mL), n-butyllithium (1.8 mL, 1.6 M in hexanes, 2.88 mmol) and trans-2-butenoyl chloride (0.60 mL, 6.3 mmol). After workup flash chromatography of the residue over silica gel (3 x 20 cm) with 96:4 hexane-ethyl acetate gave ester 199 (0.5003 g, 73.7%) as a yellow oil: IR (film) 2950, 1715, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.66-2.02 (bm, 11H; including dd at 1.90, J = 7.0, 1.5 Hz), 4.22 (s, 2H), 5.86 (dq, J = 15.5, 1.5 Hz, 1H), 6.96 (dq, J = 15.5, 7.0 Hz, 1H), 7.26-7.44 (m, 3H), 7.62-7.70 (m, 2H); exact mass, m/z 324.0634 (calcd for

$C_{16}H_{20}O_2Se$, m/z 324.0628). Anal. Calcd for $C_{16}H_{20}O_2Se$: C, 59.44; H, 6.24; O, 9.90. Found: C, 59.63; H, 6.16; O, 9.91.

(E)-[1-(Phenylseleno)cycloheptyl]methyl 2-butenoate 202:

The general procedure was followed using alcohol **200** (0.3579 g, 1.26 mmol) in THF (10 mL), n-butyllithium (1.2 mL, 1.5 M in hexanes, 1.8 mmol) and trans-2-butenoyl chloride (0.36 mL, 3.7 mmol). After workup flash chromatography of the residue over silica gel (3 x 20 cm) with 97:3 hexane-ethyl acetate gave ester **202** (0.2869 g, 64.8%) as a yellow oil: IR (film) 2880, 1722, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.46-1.82 (bm, 12H), 1.88 (dd, J = 6.5, 2 Hz, 3H), 4.08 (s, 2H), 5.84 (dq, J = 15.5, 2 Hz, 1H), 6.94 (dq, J = 15.5, 6.5, 1H), 7.22-7.42 (m, 3H), 7.58-7.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 18.0, 23.7, 30.4, 36.9, 54.4, 71.5, 122.8, 127.4, 128.8, 138.4, 144.8, 166.3, (1 peak absent from SeC_6H_5); exact mass, m/z 352.0951 (calcd for $C_{18}H_{24}O_2Se$, m/z 352.0941). Anal. Calcd for $C_{18}H_{24}O_2$: C, 61.53; H, 6.89; O, 9.11. Found: C, 61.56; H, 6.91; O, 9.22.

(E)-[1-(Phenylseleno)cyclooctyl]methyl 2-butenoate 205:

The general procedure was followed using alcohol **203** (0.2652 g, 0.892 mmol) in THF (10 mL), n-butyllithium (0.90 mL, 1.5 M in hexanes, 1.35 mmol) and trans-2-butenoyl chloride (0.27 mL, 2.8 mmol). After workup flash chromatography

of the residue over silica gel (3cm x 20 cm) with 96:4 hexane:ethyl acetate gave ester **205** (0.2340 g, 71.8%) as a yellow oil: IR (film) 2921, 1722, 1177 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.36-1.96 (bm, 17 H; including dd, at 1.90, J = 7.0, 1.5 Hz, 3H), 4.12 (s, 2H), 5.78 (dd, J = 15.5, 1.5 Hz, 1H), 6.98 (dq, J = 15.5, 7 Hz, 1H), 7.22-7.44 (m, 3H), 7.56-7.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 18.0, 23.7, 25.3, 28.5, 31.7, 55.7, 70.2, 122.8, 127.2, 128.8, 138.5, 144.7, 166.2, (1 peak absent from SeC_6H_5); exact mass, m/z 366.1105 (calcd for $C_{19}H_{26}O_2Se$, m/z 366.1098). Anal. Calcd for $C_{19}H_{26}O_2Se$: C, 62.46; H, 7.17; O, 8.76. Found: C, 62.42; H, 7.18; O, 9.02.

(E)-[4-tert-butyl-1-(Phenylseleno)cyclohexyl]methyl 2-butenoate 206:

Potassium tert-butoxide (0.070 g, 0.57 mmol) was added over 5 min from a side arm addition funnel to a stirred solution of **185** (0.1625 g, 0.50 mmol) in 3:2 THF:diethyl ether (25 mL) at -30°C. After 20 min trans-2-butenoyl chloride (0.15 mL, 1.6 mmol) was added in one portion. After a further 30 min saturated ammonium chloride (2 mL) was added. The cooling bath was removed and the mixture was allowed warm rapidly to room temperature. Brine (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with diethyl ether (20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm) with 99:1 hexane:ethyl acetate gave ester **206**

(0.1388 g, 70.6%) as a yellow solid: IR (film) 2944, 1722, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.76-1.28 (bm, 12H; including s at 0.82, 9H), 1.40-2.10 (bm, 9H; including dd at 1.90, J = 7.0, 1.5 Hz, 3H), 4.26 (s, 2H), 5.88 (dq, J = 15.5, 1.5 Hz, 1H), 7.00 (dq, J = 15.5, 7.0 Hz, 1H), 7.24-7.42 (m, 3H), 7.58-7.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 18.0, 24.2, 27.5, 32.4, 35.7, 47.1, 49.5, 66.0, 122.7, 126.6, 128.7, 138.6, 145.0, 166.3, (1 peak absent from SeC_6H_5); exact mass, m/z 394.1415 (calcd for $C_{21}H_{30}O_2Se$, m/z 394.1411). Anal. Calcd for $C_{21}H_{30}O_2Se$: C, 64.11; H, 7.69; O, 8.13. Found: C, 64.15; H, 7.71; O, 8.17.

Cyclization of Esters

4-Ethyl-2-oxaspiro[5.4]decan-3-one 174:

The general procedure for radical cyclization (p.137) was followed using ester **173** (0.1922 g, 0.570 mmol) in benzene (40 mL), triphenylstannane (0.22 mL, 0.86 mmol) in benzene (10 mL) and AIBN (0.015 g, 0.09 mmol) in benzene (10 mL) with an addition period of 8 h. After a further 7 h the solvent was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm) with 96:4 hexane-ethyl acetate yielded lactone **174** (0.0727 g, 70.0%) as a colorless oil: IR (film) 2936, 1776, 1016 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.10 (t, J = 7.5 Hz, 3H), 1.20-1.70 (bm, 12H), 2.08 (dd, J = 9, 5.5 Hz, 1H), 3.86 and 4.24 (dd, AB, J_{AB} = 8.75 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 12.6, 18.2, 22.2, 22.8, 25.5, 28.2, 35.5, 43.2,

51.5, 74.3, 179.1; exact mass, m/z 182.1306 (calcd for $C_{11}H_{18}O_2$, m/z 182.1307). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 71.88; H, 9.89.

4-Ethyl-2-oxaspiro[4.4]nonan-3-one 207:

The general procedure for radical cyclization (p.136) was followed using ester **199** (0.1790 g, 0.674 mmol) in benzene (40 mL), triphenylstannane (0.26 mL, 1.02 mmol) in benzene (10 mL) and AIBN (0.017 g, 0.10 mmol) in benzene (10 mL) with an addition period of 8 h. After a further 5 h the solvent was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm) with 96:4 and 95:5 hexane-ethyl acetate yielded lactone **207** (0.0824 g, 72.7%) as a colorless oil: IR (film) 2961, 1775, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 (t, J = 7.5 Hz, 3H), 1.42-1.80 (bm, 10H), 2.28 (dd, J = 8, 6 Hz, 1H), 3.84-4.06 (dd, AB, J_{AB} = 8.75 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 12.3, 19.3, 23.8, 24.1, 30.3, 35.7, 48.9, 50.9, 77.2, 178.9; exact mass, m/z 168.1154 (calcd for $C_{10}H_{16}O_2$, m/z 168.1150). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.44.

4-Ethyl-2-oxaspiro[6.4]undec-3-one 208:

The general procedure for radical cyclization (p.137) was followed using ester **202** (0.1916 g, 0.545 mmol) in benzene (40 mL), triphenylstannane (0.18 mL, 0.71 mmol) in benzene (10 mL) and AIBN (0.010 g, 0.06 mmol) in benzene (10 mL) with

an addition period of 8 h. After a further 6 h the solvent was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm) with 95:5 hexane-ethyl acetate yielded **208** (0.0712 g, 66.6%) as a colorless oil: IR (film) 2928, 1775, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.18 (t, J = 7.5 Hz, 3H), 1.32-1.88 (bm, 14H), 2.10 (t, J = 7Hz, 1H), 3.82 and 4.12 (dd, AB, J_{AB} = 9.25 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 12.8, 18.6, 23.0, 23.2, 29.1, 29.1, 31.5, 38.3, 46.3, 53.8, 75.7, 179.2; exact mass, m/z 196.1467 (calcd for $C_{12}H_{20}O_2$, m/z 196.1463). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.52; H, 10.32.

4-Ethyl-2-oxaspiro[7.4]dodecan-3-one 209:

The general procedure for radical cyclization (p.137) was followed using ester **205** (0.1815 g, 0.497 mmol) in benzene (40 mL), triphenylstannane (0.20 mL, 0.78 mmol) in benzene (10 mL) and AIBN (0.010 g, 0.06 mmol) in benzene (10 mL) with an addition period of 8 h. After a further 6 h the solvent was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm) with 96:4 hexane-ethyl acetate yielded lactone **209** (0.0625 g, 59.8%) as a colorless oil: IR (film) 2924, 1775, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.14 (t, J = 7.5 Hz, 3H), 1.50-1.80 (bm, 16H), 2.10 (t, J = 7 Hz, 1H), 3.82 and 4.00 (dd, AB, J_{AB}= 9.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 12.7, 19.1, 22.5, 22.8, 24.4, 27.7, 28.8, 33.7, 45.9, 53.1, 75.7, 179.3; exact mass, m/z 210.1617 (calcd for $C_{13}H_{22}O_2$, m/z 210.1620). Anal.

Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 71.33; H, 10.29.

8-tert-Butyl-4-ethyl-2-oxaspiro[5.4]decan-3-one (a mixture of isomers) 210 :

The general procedure for radical cyclization (p.137) was followed using ester **206** (0.1336 g, 0.340 mmol) in benzene (20 mL), triphenylstannane (0.11 mL, 0.43 mmol) in benzene (5 mL) and AIBN (0.010 g, 0.06 mmol) in benzene (5 mL) with an addition period of 8 h. After a further 5 h the solvent was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm) with 95:5 hexane-ethyl acetate yielded lactones **210** (0.070 g, 86.4%; two isomers in a 60:40 ratio), as a TLC pure colorless oil: IR (film) 2936, 1770, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) major isomer 0.81-1.88 (bm, 23H; including s at 0.86, 9H), 12.8 (dd, J = 11, 4.5 Hz, 1H), 3.81 and 3.93 (dd, AB J_{AB} = 9 Hz, 2H) minor isomer 0.80-1.88 (bm, 23H; including s at 0.86, 9H), 1.04 (dd, J = 9, 5.5 Hz, 1H), 3.82 and 4.22 (dd, AB J_{AB} = 9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.7, 12.8, 18.1, 19.2, 23.0, 23.9, 24.1, 27.4, 28.5, 29.3, 32.3, 35.7, 37.1, 42.1, 43.2, 47.6, 51.7, 73.7, 78.1, 179.0 (only one resonance for C=O); exact mass (isomer mixture), m/z 238.1939 (calcd for $C_{15}H_{26}O_2$, m/z 238.1933). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found (isomer mixture): C, 75.40; H, 10.98.

(E)-2-Butenyl 1-(phenylseleno)cyclohexanecarboxylate 211: *

n-Butyllithium (1.3 mL, 1.7 M in hexanes, 2.2 mmol) was added dropwise over 10 min to a stirred solution of **189** (0.8245 g, 2.09 mmol) in THF (10 mL) at -78°C. After 10 min trans-2-butenyl chloroformate (0.6 mL, 4.1 mmol) was injected rapidly and the yellow solution turned clear. The mixture was stirred at -78°C for a further 30 min and quenched with saturated ammonium chloride (10 mL). The cooling bath was removed and the mixture allowed to warm rapidly to room temperature. The organic layer was separated and the aqueous layer was extracted with diethyl ether (25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 20 cm) with 95:5 hexane-ethyl acetate yielded ester **211** (0.3242 g, 46.0%) as a clear yellow oil: IR (film) 2934, 1720, 1128 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.22-1.84 (bm, 11H, including 1.72, d, J = 6 Hz, 3H), 2.08-2.24 (m, 2H), 4.46 (d, J = 6 Hz, 2H), 5.40-5.58 (m, 1H), 5.64-5.86 (m, 1H), 7.24-7.44 (m, 3H), 7.52-7.62 (m, 2H) ; ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 17.8, 22.4, 25.4, 34.8, 51.8, 65.4, 125.3, 128.6, 129.1, 130.9, 138.0, 173.1, (1 peak absent from SeC_6H_5); exact mass, m/z 338.0788 (calcd for $C_{17}H_{22}O_2Se$, m/z 338.0785). Anal. Calcd for $C_{17}H_{22}O_2Se$: C, 60.53; H, 6.57; O, 9.49. Found: C, 60.41; H, 6.58; O, 9.74. * The ^1H NMR indicates contamination with ca. 15% of the (Z)-isomer.

(E)-2-Butenyl cyclohexanecarboxylate 213 and 4-ethyl-2-oxaspiro [5.4]decan-1-one 212: *

The general procedure for radical cyclization (p.137) was followed using ester **211** (0.2233 g, 0.662 mmol) in benzene (40 mL), triphenylstannane (0.320 g, 0.91 mmol) in benzene (10 mL) and AIBN (0.015 g, 0.09 mmol) in benzene (10 mL) with an addition period of 8 h. After a further 8 h the solvent was evaporated and Kugelrohr distillation of the residue (140°C, 0.1 mm) yielded a mixture of **213** and **212**. Flash chromatography over silica gel (2 x 20 cm) with 98:2 and 96:4 hexane-ethyl acetate yielded crude lactone **212** and ester **213** (0.0188 g, 15.6%) as a colorless oil: Kugelrohr distillation of the crude lactone (50°C, 0.1 mm) yielded **212** (0.0410 g, 34.0%) as a colorless oil: **213** had: IR (film) 2934, 1733, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.16-2.02 (bm, 13H; including d at 1.76), 2.34 (bm, 1H), 4.52 (d, J = 7 Hz, 2H), 5.50-5.90 (bm, 2H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 17.7, 25.5, 25.8, 29.1, 43.3, 64.8, 125.4, 130.8, 175.8; exact mass, m/z 182.1305 (calcd for $C_{11}H_{18}O_2$, m/z 182.1307) * ^1H NMR indicates contamination by ca. 20% of the (Z)-isomer peak, at 4.66 (d, J = 7 Hz). **212** had: IR (film) 2933, 1771, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, J = 7.5 Hz, 3H), 1.24-1.84 (bm, 11H), 1.96-2.22 (bm, 2H), 3.97 and 4.33 (dd, AB of ABX, J_{AB} = 9.25 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 12.0, 20.5, 21.7, 22.0, 23.5, 25.6, 27.6, 32.7, 46.3, 69.1, 181.2; exact mass, m/z 182.1306 (calcd for $C_{11}H_{18}O_2$, m/z 182.1307). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 71.62; H, 9.41.

General Procedure for the Preparation of the β-hydroxy Esters 233, 237 and 240:

Lithium diisopropylamide (LDA) was prepared by dropwise addition of n-butyllithium [1.05-1.1 equiv., in hexanes (Aldrich)] to a cold (- 78°C), stirred solution of diisopropylamine (1.2-1.4 equiv.) in THF. The solution was warmed to 0°C (ice bath). Stirring was continued for 20-30 min and the solution was then cooled to - 78°C. The ester (1 equiv.) in THF (1-2 mL) was added dropwise over ca 10 min and, after a further 20-30 min, freshly purified (by flash chromatography and distillation) (phenylseleno)acetaldehyde (1.25-1.5 equiv.) in THF (1-2 mL) was injected rapidly. Stirring at - 78°C was continued for 5-10 min and then glacial acetic acid (ca. 1.5 equiv.) in THF (1-2 mL) was injected. The cooling bath was removed and the solution was allowed to warm to room temperature. Water was added, the organic layer was separated, and the aqueous layer extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was processed as described in individual experiments.

Methyl 2-(2-cyclopenten-1-yl)-3-hydroxy-4-(phenylseleno)butanoate (a mixture of isomers) 233:

The general procedure was followed using ester 232 (0.889 g, 6.43 mmol) in THF (5 mL), LDA [from diisopropylamine (1.1 mL, 7.8 mmol) and n-butyllithium

(4.4 mL, 1.6 M in hexanes, 7.0 mmol)] in THF (15 mL), (phenylseleno)acetaldehyde (1.533 g, 8.14 mmol) in THF (5 mL), and glacial acetic acid (0.50 g, 8.3 mmol) in THF (5 mL). After workup, flash chromatography of the residue over silica gel (5 x 15 cm) with 85:15 hexane-ethyl acetate yielded **233** (1.5921 g, 71.1%; a mixture of 4 diastereoisomers, 2 major isomers and 2 minor isomers) as a yellow oil. The mixture could be separated by chromatography over silica gel with 80:20 petroleum ether (bp 30-60°C):diethyl ether into three fractions (F1-F3 inclusive): F1 (major isomer) IR (hexane cast) 3480, 1728, 1437, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.64 (m, 1H), 1.98 (m, 1H), 2.26 (m, 2H), 2.71 (t, J = 7 Hz, 1H), 2.81 (bs, 1H), 2.99 (dd, AB of ABX J_{AB} = 13 Hz, 1H), 3.16 (m, 1H), 3.24 (dd, AB of ABX J_{AB} = 13 Hz, 1H), 3.64 (s, 3H), 3.93 (m, 1H), 5.55 (m, 1H), 5.74 (m, 1H), 7.27 (m, 3H), 7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 26.8, 31.6, 34.5, 45.2, 51.5, 55.1, 69.5, 127.4, 129.0, 129.3, 131.9, 132.3, 132.9, 173.6; exact mass, m/z 340.0575 (calcd for $C_{16}H_{20}O_3Se$, m/z 340.0578). F2 (major isomer) had IR (hexane cast) 3440, 1728, 1430, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56 (m, 1H), 1.98 (m, 1H), 2.27 (m, 2H), 2.65 (t, J = 7 Hz, 1H), 2.87 (s, 1H), 3.00 (dd, AB of ABX J_{AB} = 13 Hz, 1H), 3.14 (m, 1H), 3.25 (dd, AB of ABX J_{AB} = 13 Hz, 1H), 3.66 (s, 3H), 3.96 (m, 1H), 5.59 (m, 1H), 5.77 (m, 1H), 7.27 (m, 3H), 7.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 28.4, 32.0, 34.0, 44.8, 51.6, 55.6, 69.8, 127.4, 129.1, 129.3, 131.8, 132.2, 132.9, 173.7 ; exact mass, m/z 340.0581 (calcd for $C_{16}H_{20}O_3Se$, m/z 340.0578). F3 (a 1:1 mixture of the two minor isomers) had IR

(hexane cast) 3480, 1731, 1713, 1437, 1167, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (data for 2 isomers) δ 1.52 (m, 1H), 1.64 (m, 1H), 1.98 (m, 1H), 2.12 (m, 1H), 2.34 (bm, 4H), 2.66 (dd, J = 8.5, 4.0 Hz, 1H), 2.72 (dd, J = 8.5, 4.5 Hz, 1H), 2.96-3.12 (bm, 7H), 3.34 (bs, 1H), 3.67 and 3.69 (s, 6H), 3.92 (bs, 2H), 5.54 (m, 1H), 5.70 (m, 1H), 5.80 (m, 2H), 7.26 (m, 6H), 7.52 (m, 4H) ; ^{13}C NMR ($CDCl_3$, 75.47 MHz) (data for 2 isomers) δ 27.2, 28.4, 31.8, 34.1, 34.3, 45.2, 45.6, 51.6, 51.6, 54.0, 54.0, 70.3, 70.7, 127.3, 129.2, 129.4, 131.6, 131.8, 132.5, 132.6, 133.2, 174.5, 174.8 (1 methylene peak coincident) ; exact mass (isomer mixture), m/z 340.0584 (calcd for $C_{16}H_{20}O_3Se$, m/z 340.0578). Anal. Calcd for $C_{16}H_{20}O_3Se$: C, 56.64; H, 5.94; O, 14.15. Found (total reaction product): C, 56.41; H, 5.84; O, 13.89.

Methyl 2-(2-cyclohexen-1-yl)-3-hydroxy-4-(phenylseleno)butanoate (a mixture of isomers) 237:

The general procedure was followed using ester **236** (0.9925 g, 6.44 mmol) in THF (3 mL), LDA [made from diisopropylamine (1.2 mL, 8.6 mmol) and n-butyllithium (4.6 mL, 1.5 M in hexanes, 6.9 mmol)] in THF (50 mL), (phenylseleno)acetaldehyde (1.62 g, 8.14 mmol) in THF (3 mL), and glacial acetic acid (0.50 g, 8.3 mmol) in THF (5 mL). After workup, flash chromatography of the residue over silica gel (4 x 20 cm) with 90:10 hexane-ethyl acetate and chromatography

again (3 x 15 cm) with 85:15 hexane-ethyl acetate yielded **237** (1.9132 g, 84.1%; a mixture of four diastereoisomers, 2 major and 2 minor) as a light yellow oil: The mixture could be separated by chromatography over silica gel with 80:20 petroleum ether (bp 30-60°C):diethyl ether into three fractions (F1-F3 incl.): F1 (major isomer) IR (hexane cast) 3480, 1729, 1437, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36 (m, 1H), 1.50 (m, 1H), 1.71 (bm, 2H),1.93 (bm, 2H), 2.69 (bm, 2H), 2.79 (bs, 1H), 3.00 and 3.24 (dd, AB of ABX J_{AB} = 13 Hz, 2H), 3.64 (s, 3H), 4.00 (m, 1H), 5.44 (dm, J = 10 Hz, 1H), 5.68 (m, 1H), 7.27 (m, 3H), 7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 21.2, 25.0, 25.7, 34.6, 34.9, 51.4, 55.4, 68.3, 127.4, 128.6, 129.0, 129.0, 129.3, 132.9, 173.3; exact mass, m/z 354.0735 (calcd for $C_{17}H_{22}O_3Se$, m/z 354.0735). F2 (major isomer) had IR (hexane cast) 3440, 1721, 1435, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36 (m, 1H), 1.50 (m, 1H), 1.67 (m, 2H), 1.94 (m, 2H), 2.61 (t, J = 7 Hz, 1H), 2.69 (m, 1H), 2.38 (d, J = 3.5 Hz, 1H), 2.98 and 3.20 (dd, AB of ABX J_{AB} = 12.5 Hz, 2H), 3.65 (s, 3H), 4.05 (m, 1H), 5.55 (dm, J = 10 Hz, 1H), 5.71 (m, 1H), 7.26 (m, 3H), 7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 21.7, 25.0, 27.6, 34.3, 34.8, 51.5, 55.6, 68.3, 127.3, 127.8, 128.8, 129.1, 129.2, 132.9, 173.4; exact mass, m/z 354.0747 (calcd for $C_{17}H_{22}O_3Se$, m/z 354.0735). F3 (a 1:1 mixture of the two minor isomers) had IR (hexane cast) 3480, 1729, 1437, 1167, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (data for 2 isomers) δ 1.34 (m, 2H), 1.52 (m, 2H), 1.68 (m, 3H), 1.81 (m, 1H), 1.97 (m, 4H), 2.65 (m, 4H), 2.94 (m, 2H), 3.07 (m, 2H), 3.26 (m, 2H), 3.68 (s, 3H), 3.70 (s, 3H), 4.00 (bm,

2H), 5.39 (dm, J = 11 Hz, 1H), 5.63 (dm, J = 10 Hz, 1H), 5.74 (m, 2H), 7.26 (m, 6H), 7.55 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) (data for 2 isomers) δ 20.7, 21.3, 25.1, 26.6, 26.7, 34.1, 34.3, 34.6, 35.3, 51.6, 51.6, 53.8, 54.0, 62.3, 127.3, 127.3, 127.8, 128.2, 129.2, 129.2, 129.3, 129.5, 133.1, 133.2, 174.8, 174.9 (1 peak coincident for methylene resonances and one signal for OCH_3) ; exact mass (isomer mixture), m/z 354.0746 (calcd for $C_{17}H_{22}O_3Se$, m/z 354.0735). Anal. Calcd for $C_{17}H_{22}O_3Se$: C, 57.79; H, 6.28; O, 13.59. Found (total reaction product): C, 57.59; H, 6.29; O, 13.36.

Ethyl 3-hydroxy-4-(phenylseleno)-2-(1'S*,R*-6'S*,R*-6-tert-butyl-2-cyclohexen-1-yl)butanoate (a mixture of isomers) 240:

The general procedure was followed using ester **239** (0.1953 g, 0.87 mmol) in THF (2 mL), LDA [from diisopropylamine (0.17 mL, 1.2 mmol) and n-butyllithium (0.7 mL, 1.6 M in hexanes, 1.1 mmol)] in THF (10 mL), (phenylseleno)acetaldehyde (0.25 g, 1.26 mmol) in THF (2 mL), and glacial acetic acid (0.070 g, 1.2 mmol) in THF (1 mL).After workup, flash chromatography of the residue twice over silica gel (3 x 20 cm) with 90:10 hexane-ethyl acetate yielded **240** (0.345 g, 93.6%; a mixture of four diastereoisomers, 2 major isomers and 2 minor isomers) as a light yellow oil: IR (hexane cast) 3500, 1725, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (data for total product, approximate intergrals) δ 0.88 and 0.92 (s, 36H), 1.15-1.30 (bm, 16H),

1.45-2.05 (bm, 16H), 2.50-3.38 (bm, 20H), 3.90-4.25 (bm, 12H), 5.45-5.50 (bm, 2H), 5.65-5.85 (bm, 2H), 5.78 (m, 4H) 7.25 (m, 12H), 7.52 (m, 8H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) (data for total product) δ 14.2, 14.3, 14.4, 20.3, 20.3, 20.5, 21.5, 22.6, 22.7, 22.9, 28.8, 29.0, 29.0, 33.5, 33.6, 33.7, 33.8, 34.1, 34.2, 34.3, 34.4, 35.2, 43.3, 43.4, 43.9, 44.3, 53.6, 55.1, 56.9, 57.6, 60.3, 60.5, 60.7, 60.8, 68.6, 68.9, 69.7, 127.2, 127.5, 127.6, 127.8, 128.0, 129.0, 129.1, 129.2, 129.4, 129.5, 129.7, 132.8, 132.2, 133.3, 133.5, 172.9, 173.2, 174.9; exact mass (isomer mixture), m/z 424.1506 (calcd for $C_{22}H_{32}O_3Se$, m/z 424.1517). Anal. Calcd for $C_{22}H_{32}O_3Se$: C, 62.40; H, 7.62; O, 11.33. Found (for total reaction product): C, 62.54; H, 7.56; O, 11.20.

trans-4-tert-Butyl-2-cyclohexen-1-ol **244**:[129]

A 250 mL flask containing a magnetic stirring bar was charged with aluminum tri(2-propanolate) [11.5 g, 56.3 mmol, (Aldrich Gold Label)], 4-tert-butyl-2-cyclohexen-1-one **245**[128] (2.85 g, 18.7 mmol) and dry 2-propanol (125 mL). The flask was then fitted with a short condenser (30 cm) carrying a short path distillation apparatus fitted with a thermometer and receiver. The apparatus was protected from moisture with a drying tube (Drierite). The stirred solution was heated in an oil bath to ca. 105-108 °C at which point 2-propanol slowly distilled into the receiver. Fractions were collected every 0.5 h and tested with 2,4-dinitrophenylhydrazone solution for the

presence of 2-propanone. After 5.5 h no more 2-propanone was present in the distillate. The mixture was cooled and the remaining 2-propanol was evaporated. The residue was cooled to 0 °C and quenched with ice-cold aqueous hydrochloric acid (130 mL, 1.5 M). The resulting solution was saturated with salt and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (2 x 50 mL), dried ($MgSO_4$) and evaporated to yield a mixture of cis- and trans-4-tert-butyl-2-cyclohexen-1-ol **244** and **246** (2.78 g, 96%, 22:78 by ^1H NMR) as a golden brown oil which solidified upon standing. ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 and 0.91 (s, 18H, ratio 78:22), 1.10-2.00 (bm, 10H), 2.10 (m, 2H), 4.08-4.24 [bm, 2H, including peaks at 4.20 (major) and 4.08 (minor)], 5.70-6.00 (m, 4H).

The mixture of cis- and trans-4-tert-butyl-2-cyclohexen-1-ols (2.87 g, 18.00 mmol) was dissolved in pyridine (20 mL) and p-nitrobenzoyl chloride (5.00 g, 2.69 mmol) was added in portions over 5 min. After being stirred for 2 h at room temperature the mixture was quenched by pouring the solution, with rapid stirring, into a mixture of concentrated hydrochloric acid (25 g) and ice (200 g). The resulting aqueous solution was extracted with diethyl ether (2 x 100 mL) and the combined organic extracts were washed with saturated aqueous sodium bicarbonate (2 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 10 cm) with 90:10 hexane-ethyl acetate yielded a mixture of the p-nitrobenzoates of **244** and **246** (5.13 g, 94%).

The material was crystalized twice from methanol to yield the p-nitrobenzoate of 244 (1.98 g) as a light yellow solid: mp 92-94°C (lit.[129] mp 88-91°C).

Potassium hydroxide (1.50 g, 26.7 mmol) was added to a stirred solution of the p-nitrobenzoate of **244** in methanol (15 mL) and water (3 mL). After 40 min at room temperature no starting material remained (TLC). The mixture was poured into water (100 mL), saturated with salt, and extracted with diethyl ether (2 x 75 mL). The organic extracts were combined, dried (Na_2SO_4) and evaporated to yield **244** (0.93 g, 92%). The product was homogenous by TLC (5 cm plate, developed four times in 95:5 hexane-ethyl acetate) and > 99% pure trans-isomer by VPC (OV-1, 150°C): IR (CH_2Cl_2 cast) 3320, 2959, 1566, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (s, 9H), 1.32 (bm, 3H), 1.78 (m, 1H), 1.88 (m, 1H), 2.14 (m, 1H), 4.18 (bs, 1H), 5.84 (m, 2H); exact mass, m/z 154.1360 (calcd for $C_{10}H_{18}O$, m/z 154.1358). Lit.[129] mp 31-32°C.

1-Ethoxy, 1-[(trans-4-tert-butyl)-2-cyclohexen-1-yloxy]-2-(phenylseleno) ethane 247 (a mixture of two isomers):

Phenylselenenyl bromide (1.150 g, 4.87 mmol) in THF (20 mL) was decolorised by the addition of ethyl vinyl ether (0.5 mL, 5.2 mmol). Trans-4-tert-butyl-2-cyclohexen-1-ol **244** (0.494 g, 3.20 mmol) in THF (7 mL) was injected dropwise followed by diisopropylamine (0.75 mL, 5.4 mmol). Stirring was continued

for 15 min at room temperature by which time a white percipitate had formed. The reaction mixture was then poured into water (50 mL) and saturated aqueous sodium bicarbonate (50 mL). The resulting mixture was extracted with diethyl ether (3 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm) with 98.5:1.5 hexane-ethyl acetate (0.5 L) followed by 98:2 hexane-ethyl acetate (1.5 L) yielded a light yellow oil which was further purified by centrifugal chromatography (Chromatotron, 4mm plate, Merck silica gel 60 PF_{254}) to yield **247** (1.10 g, 90%; a 1:1 mixture of isomers) as a TLC pure, pale yellow oil: IR (hexane cast) 2959, 1073, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (s, 18H), 1.16 (bm, 8H; including d at 1.18, J = 4 Hz, 6H), 1.40-1.60 (m, 2H), 1.84 (m, 2H), 1.90 (m, 2H), 2.10 (m, 2H), 3.10 (m, 4H), 3.50-3.70 (bm, 4H), 4.16 (m, 2H), 4.84 (t, J = 5 Hz, 2H), 5.68-5.82 (bm, 4H), 7.20 (m, 6H), 7.48 (m, 4H); ^{13}C NMR ($CDCl_3$; 75.47 MHz) δ 15.2, 22.7, 22.9, 27.1, 30.0, 30.7, 31.6, 31.6, 32.1, 32.8, 45.9, 61.0, 72.4, 72.7, 101.0, 101.6, 126.8, 129.0, 129.8, 130.3, 130.6, 130.6, 131.6, 131.7, 132.4, 132.5; exact mass (isomer mixture), m/z 382.1405 (calcd for $C_{20}H_{30}O_2Se$, m/z 382.1411). Anal. Calcd for $C_{20}H_{30}O_2Se$: C, 62.98; H, 7.93; O, 8.39. Found (isomer mixture): C, 62.81; H, 7.93; O, 8.50.

Ethyl (trans-6-tert-butyl-2-cyclohexen-1-yl)acetate 239:

Sodium bicarbonate (0.265 g, 3.15 mmol) and sodium metaperiodate (0.920 g, 4.32 mmol) were added to a solution of **247** (1.0962 g, 2.87 mmol) in 6:1 methanol:water (90 mL). After 1 h at room temperature the reaction mixture was poured into water (100 mL) and the solution was extracted with dichloromethane (4 x 50 mL). The combined organic extracts were dried (K_2CO_3) and evaporated. The resulting selenoxide (**249**) was dissolved in anhydrous toluene (30 mL), and n-hexylamine (1.1 mL, 8.3 mmol) was added. The solution was refluxed for 18 h under argon. The toluene and most of the n-hexylamine were removed under reduced pressure. Flash chomatography of the residue over silica gel (4 x 20 cm) with 98.5:1.5 hexane-ethyl acetate and rechromatography over silica gel (3 x 20 cm) with 98:2 hexane-ethyl acetate gave the crude product. Kugelrohr distillation (75°C, 0.1 mm) yielded **239** as a clear liquid (0.361 g, 56.0%): IR (film) 2958, 1736, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 (s, 9H), 1.28 (m, 4H; including t at 1.28 J = 7 Hz, 3H), 1.54-1.76 (m, 2H), 1.82-2.06 (bm, 2H), 2.35 (m, 2H), 2.56 (bs, 1H), 4.12 (m, 2H), 5.64 (m, 1H), 5.72 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.4, 21.1, 23.0, 28.9, 32.3, 33.9, 42.3, 45.5, 60.3, 128.0, 130.7, 172.9; exact mass, m/z 224.1777 (calcd for $C_{14}H_{24}O_2$, m/z 224.1776). Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.96; H, 10.78. Found: C, 75.22; H, 11.06.

Methyl (3aα,6aα)-octahydro-2-hydroxypentalene-1-carboxylate (a mixture of isomers) 235:

The general procedure for radical cyclization (p.137) was followed using **233** (0.208 g, 0.613 mmol) in benzene (30 mL), triphenylstannane (0.21 mL, 0.82 mmol) in benzene (5 mL), AIBN (0.015 g, 0.09 mmol) in benzene (5 mL) and an addition period of 9 h. After a further 9 h the solvent was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm) with 90:10, 85:15, 80:20, 75:25 and 70:30 hexane-ethyl acetate (100 mL of each solvent system) yielded three fractions: F1 (0.0493 g, 44.0%), F2 (0.0269 g, 24.1%) and F3 (0.0244 g, 21.8%; a 1:1 mixture of isomers) which were subsequently identified as stereoisomers of **235**. F1 had: IR (hexane cast) 3520, 1716, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (m, 1H), 1.44-1.94 (m, 7H), 2.54 (m, 1H), 2.78 (m, 2H), 2.64 (s, 1H), 2.72 (s, 3H), 4.42 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 27.8, 31.1, 35.0, 39.8, 42.5, 45.5, 51.5, 51.8, 75.2, 175.4; exact mass, m/z 184.1102 (calcd for $C_{10}H_{16}O_3$, m/z 184.1099). F2 had: IR (hexane cast) 3440, 1735, 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (m, 1H), 1.32 (m, 1H), 1.40-1.68 (m, 6H), 2.04 (dd, J = 15, 7 Hz, 1H), 2.28 (bs, 1H), 2.78 (bs, 1H), 3.26 (s, 1H), 3.70 (s, 3H), 4.44 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 24.8; 32.3, 33.1, 41.4, 41.4, 45.4, 51.8, 55.5, 75.8, 175.9; exact mass, m/z 184.1103 (calcd for $C_{10}H_{16}O_3$ m/z 184.1099). F3 had: IR (hexane cast) 3493, 3476, 1739, 1718, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (data for both isomers) δ 1.08-1.88 (bm, 15H; including bs at 1.66, 6H), 1.96 (m, 1H), 2.22-2.64

(bm, 6H), 3.74 (m, 2H), 3.76 and 3.78 (s, 6H, ratio 1:1), 4.24 (m, 1H), 4.44 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (data for both isomers) δ 24.7, 27.1, 30.8, 32.9, 33.4, 35.5, 38.4, 39.0, 39.4, 40.8, 43.1, 44.3, 51.4, 51.7, 56.0, 58.5, 72.6, 75.5, 174.4, 175.4; exact mass (isomer mixture), m/z 184.1088 (calcd for $C_{10}H_{16}O_3$, m/z 184.1099). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found (total reaction product): C, 64.87; H, 8.88.

Methyl (3aα,7α)-octahydro-2-hydroxyindene-1-carboxylate (a mixture of isomers) 238:

The general procedure for radical cyclization (p.137) was followed using **237** (0.2073 g, 0.587 mmol) in benzene (30 mL), triphenylstannane (0.20 mL, 0.78 mmol) in benzene (5 mL), AIBN (0.015 g, 0.09 mmol) in benzene (5 mL) and an addition period of 9 h. After a further 10 h the solvent was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm) with 95:5, 90:10, 80:20 and 70:30 hexane-ethyl acetate (100 mL of each solvent system) yielded two fractions: F1 (0.047 g, 40.4%) and F2 (0.0597 g, 51.2%) which were subsequently identified as stereoisomers of **238**. F1 had: IR (hexane cast) 3480, 1711, 1171 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (m, 1H), 1.34-1.80 (bm, 8H), 2.02 (bs, 1H), 2.14 (m, 2H), 2.68 (t, J = 6.5 Hz, 1H), 3.70 (s, 3H), 4.14 (s, 1H), 4.48 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.3, 24.1, 25.3, 26.5, 36.7, 36.8, 41.4, 51.5, 53.1, 71.7,

174.5; exact mass, m/z 198.1255 (calcd for $C_{11}H_{18}O_3$, m/z 198.1256). F2 (a mixture of 3 isomers, 1 major and 2 minor) had: IR (hexane cast) 3440, 1736, 1436 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (major isomer) δ 1.0 (m, 1H), 1.14-1.50 (m, 3H), 2.56 (bs, 4H), 1.80 (m, 2H), 2.14 (m, 1H), 2.50 (se, J = 6 Hz, 1H), 2.84 (dd, J = 10, 6 Hz, 1H), 2.94 (d, J = 5 Hz, 1H), 3.72 (s, 3H), 4.52 (m, 1H); peaks for the minor isomers at δ 1.90 (bs), 1.98 (m), 2.32 (bs), 2.44 (bs), 2.70 (dd, J = 10, 6 Hz), 3.68 (s), 3.70 (s), 4.78 (m); ^{13}C NMR ($CDCl_3$, 74.47 MHz) (major isomer) δ 21.4, 24.3, 26.2, 29.1, 36.6, 39.9, 41.6, 51.0, 51.7, 72.9, 174.8; peaks for minor isomers at δ 18.8, 20.2, 22.2, 24.1, 24.9, 26.6, 26.9, 28.9, 35.4, 37.0, 37.4, 39.8, 41.9, 42.2, 51.5, 51.8, 59.1, 73.2, 76.3, 173.8, 175.9; exact mass, m/z 198.1253 (calcd for $C_{11}H_{18}O_3$, m/z 198.1256). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found (total reaction product): C, 66.69; H, 9.23.

Ethyl (1β,2β,3aα,7β,7aα)-octahydro-7-tert-butyl-2-hydroxy-2H-indene-1-carboxylate 241a and Ethyl (1β,2α,3aα,7β,7aα)-octahydro-7-tert-butyl-2-hydroxy-2H-indene-1-carboxylate 241b:

The general procedure for radical cyclization (p.137) was followed using **240** (0.1460 g, 0.345 mmol) in benzene (30 mL), triphenylstannane (0.11 mL, 0.43 mmol) in benzene (5 mL), AIBN (0.015 g, 0.09 mmol) in benzene (5 mL) and an addition period of 9 h. After a further 5.5 h the solvent was evaporated and flash

chromatography of the residue over silica gel (2 x 20 cm) with 80:20 hexane-ethyl acetate yielded **241** (0.0661 g, 71.4%; 2 major isomers and 2 minor isomers). The ^1H NMR spectrum of the total reaction product indicates (on the basis of the tert-butyl resonances) four isomers in a ratio 60:30:5:5. Partial separation of the two major fractions [**241a** (60%) and **241b** (30%)] was possible by careful chromatography. **241a** had: IR (hexane cast) 3440, 1730 (shoulder 1715), 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84-1.04 [bm, 10H; including s at 0.94, $C(CH_3)_3$], 1.28 (m, 4H including t at 1.28, J = 7Hz, OCH_2CH_3), 1.35-1.58 (bm, 4H), 1.70 (m, 1H), 1.76 (m, 1H,), 1.88 (m, 1H C_3-H), 2.18 (m, 1H C_{3a}-H), 2.60 (ddd, J = 10, 6.5, 2.5 Hz, 1H, C_{7a}-H), 2.72 (d, J = 6 Hz, 1H, -O-H), 2.90 (dd, J = 10, 7 Hz, 1H, C_1-H), 4.18 (ddd, J = 14, 7, 1.5 Hz, 2H, O-CH_2CH_3), 4.46 (q, J = 6.5 Hz, 1H, C_2-H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 14.4 (CH_3), 21.8 (C-5*), 23.1 (C-6*), 29.3 (C-7*), 29.7 [$C(CH_3)_3$], 34.2 (C-4‡), 35.3 (C-3‡), 40.8 (C-3_a), 42.8 (C-7_a), 43.8 [$C(CH_3)_3$], 53.6 (C-1), 60.6 (OCH_2CH_3), 72.0 C-2), 174.5 (C=O); Nuclear Overhauser enhancements (±0.5%) between C_1-H and C_2-H = 11.0%, C_{7a}-H and C_{3a}-H = 7.0 %, C_{3a}-H and C_{7a}-H = 7.0 %. **241b** had: IR (CCl_4) 3480, 2880, 1730, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 [s, 9H, $C(CH_3)_3$], 1.26 (t, 3H, OCH_2CH_3), 1.30-1.68 (bm, 8H), 2.98 (bs, 1H, OH), 2.08 (bs, 1H, C_{3a}-H), 2.16 (m, 1H, C_3-H), 2.38 (ddd, J = 10, 6.25, 4 Hz, 1H, C_{7a}-H), 2.82 (dd, J = 10, 6.5 Hz, 1H, C_1-H), 4.14 (m, 2H, OCH_2CH_3), 4.40 (bs, 1H, C_1-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (by subtraction of spectrum for **241a** from spectrum of combined **241a**

and **241b**) δ 21.9 (C-5*), 23.6 (C-6*), 29.6 (C-7*), 29.6 [$C(CH_3)_3$], 34.1 (C-4‡), 36.5 (C-3‡), 41.1 ($C-3_a$), 42.4 ($C-7_a$), 43.7 [$C(CH_3)_3$], 58.6 (C-1), 60.5 (OCH_2CH_3), 75.6 (C-2), 175.6 (C=O); Nuclear Overhauser enhancements (±0.5%) between C_{7a}-H and C_2-H = 3.0%, C_{7a}-H and C_{3a}-H = 5.5%, C_{3a}-H and C_2-H = 6.5%, C_{3a}-H and C_{7a}-H = 7.0%; exact mass (isomer mixture), m/z 268.2033 (calcd for $C_{16}H_{28}O_3$, m/z 268.2038). Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found (isomer mixture): C, 71.32; H, 10.36. Note, * and ‡ assignments may be interchanged.

1H-Imidazole-1-carbothioic acid O-[methyl 2-([3aα,7aα]-octahydro-2H-indene-1-carboxylate)] (a mixture of isomers) 243:

Thiocarbonyldiimidazole (0.130 g, 0.73 mmol) was added to a stirred solution of **238** (0.049 g, 0.25 mmol) in dichloromethane (3 mL), and the solution was refluxed for 12 h. The solvent was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm) with 70:30 hexane-ethyl acetate yielded **243** (0.073 g, 96%): IR (hexane cast) 2926, 1740, 1389, 1332, 1287, 1231 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00-1.40 (bm, 3H), 1.42-2.34 (bm, 8H; including bs at 1.68), 2.46 (m, 0.5H), 2.72 (m, 0.5H), 3.02 (m, 0.2H), 3.10 (t, 0.3H), 3.20 (dd, 0.5H), 3.60-3.70 (m, 3H; including s at 3.60, 3.62 and 3.70, 3H), 6.00 (m, 1H), 7.00 (d, 1H), 7.54-7.62 (m, 1H), 8.28 (m, 1H); Mass (EI) 308, 241, 180, 149, 121, exact mass

calculated for $C_{15}H_{20}N_2O_3S$, m/z 308.1194.

Methyl (1α,3aα,7aα)-octahydro-2H-indene-1-carboxylate and methyl (1β,3aα,7aα)-octahydro-2H-indene-1-carboxylate 242:

A solution of **243** (0.0675 g, 0.22 mmol) and AIBN (0.002 g, 0.01 mmol) in THF (5mL) was added dropwise over 40 min to a refluxing solution of tributyltin hydride (0.089 g, 0.31 mmol) in THF (4 mL). After a further 1 h no starting material remained (TLC), however the product could not be visualised (TLC) by our methods of development. The solvent was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm) with 97:3 hexane-ethyl acetate gave fractions which were analyzed by VPC (OV-1, 225 °C). The appropriate fractions were combined and evaporated to yield **242** (0.0323 g, 80.6%) as a clear colorless oil: IR (hexane cast) 2927, 1736, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (data for both isomers) δ 1.00-2.20 (bm, 28H; including bs at 1.54), 2.70 and 2.88 (m, 2H; ratio 65:35), 3.66 and 3.67 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (data for both isomers) δ 20.6, 22.5, 23.3, 24.1, 25.3, 25.6, 26.8, 26.9, 27.2, 27.9, 30.1, 39.5, 39.6, 42.7, 43.8, 46.0, 49.0, 51.2, 51.5, 174.8, 177.4 (1 peak absent); exact mass (isomer mixture), m/z 182.1305 (calcd for $C_{11}H_{18}O_2$, m/z 182.1307). ^{13} C NMR data for the authentic sample of esters[126] ($CDCl_3$, 100.6 MHz) δ 20.6, 23.3, 24.1, 25.2, 25.6, 26.8, 27.1,

27.9, 30.0, 39.6, 42.7, 43.8, 48.9, 51.1, 174.8.

Methyl 2-(2-cyclohexen-1-yl)-3-oxooctanoate (a mixture of isomers) 252:

Lithium isopropylcyclohexylamine (LiICA) was freshly prepared by the dropwise addition of n-butyllithium [1.62 mL, 1.6M in hexanes (Aldrich), 2.59 mmol] to a stirred solution of N-isopropylcyclohexylamine (0.43 mL, 2.61 mmol) in THF (10 mL) at -78°C. The solution was warmed to 0°C and stirring was continued for 20-30 min. The solution was then cooled to -78°C. Ester **236** (0.200 g, 1.30 mmol) was added dropwise over ca. 5 min and, after a further 15 min, freshly distilled hexanoyl chloride (0.175 g, 1.30 mmol) in THF (1 mL) was injected rapidly. Stirring at -78°C was continued for 10 min and then concentrated hydrochloric acid (0.170 g, 1.7 mmol) in THF (2 mL) was added in one portion. The cooling bath was removed and the solution was allowed to warm to room temperature. Brine (10 mL) was added, the organic layer was separated and the aqueous layer extracted with diethyl ether (25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel with 97:3 hexane-ethyl acetate yielded **252** (0.175 g, 53.3%; a 1:1 mixture of 2 isomers) as a clear liquid: IR (hexane cast) 1750, 1710, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (data for both isomers) δ 0.88

(t, J = 7 Hz, 6H), 1.28 (m, 10H), 1.50-1.72 (bm, 10H), 1.98 (bs, 4H), 2.52 (m, 4H), 2.98 (m, 2H), 3.41 (d, J = 5.5 Hz, 1H), 3.44 (d, J = 5.5 Hz, 1H), 3.72 (s, 6H), 5.38 (d, J = 10 Hz, 1H), 5.48 (d, J = 10 Hz, 1H), 5.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) (data for both isomers) δ 13.9, 20.7, 20.9, 22.4, 23.0, 25.0, 25.0, 26.7, 31.2, 35.2, 35.2, 43.0, 43.1, 52.2, 64.3, 64.4, 127.4, 127.8, 129.5, 129.7, 169.2, 169.3, 204.7, 204.8; exact mass (isomer mixture), m/z 252.1727 (calcd for $C_{15}H_{24}O_3$, m/z 252.1725).

Trimethylsilyl (phenylthio)acetate 254:

Chlorotrimethylsilane (2.20 mL, 17.3 mmol) was added dropwise over 5 min to a stirred solution of (phenylthio)acetic acid[133] (10.0 g, 59.4 mmol) and hexamethyldisilazane (9.2 mL, 43.6 mmol) in pyridine (10 mL) at room temperature. After being stirred for 12 h, the reaction mixture was diluted with petroleum ether (50 mL, bp. 30-60°C, reagent grade) and the white precipitate was removed by filtration through a Celite pad (10 x 1 cm). After evaporation (30°C, 15 mm) of the solvent distillation of the residue yielded **254** [10.6 g, >99% pure (VPC OV-I, 180°C), 74.2%] as a clear colorless liquid: bp 125°C, 0.2 mm; IR (hexane cast) 1704, 1439, 1267, 890, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.26 (s, 9H), 3.64 (s, 2H), 7.22 (m, 1H), 7.30 (m, 2H), 7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ - 0.4,

38.3, 126.8, 129.0, 130.1, 135.5, 169.6; exact mass, m/z 240.0640 (calcd for $C_{11}H_{16}O_2SSi$, m/z 240.0640).

3-(2-Cyclopenten-1-yl)-1-(phenylthio)propan-2-one 256 by reaction between trimethylsilyl 2-lithio-(phenylthio)acetate 254 and 255.

Ester **254** (0.3126 g, 1.30 mmol) was added dropwise in THF (2 mL) over ca. 5 min to a stirred solution of LiICA [made from N-isopropylcyclohexylamine (0.47 mL, 2.9 mmol) and n-butyllithium (1.7 mL, 1.6 M in hexanes, 2.7 mmol)] in THF (10 mL) at - 78°C. After 10 min the acid chloride **255** (0.205 g, 1.42 mmol) in THF (2 mL) was injected rapidly. Stirring at - 78°C was continued for a further 5 min and then concentrated hydrochloric acid (0.35 g, 3.6 mmol) in THF (2 mL) was injected. The cooling bath was removed and the solution was allowed to warm to room temperature over 15 min. The solvent was evaporated, dioxane (10 mL) was added followed by dilute hydrochloric acid (1 N) until the dioxane solution was acidic (pH 1-2). The mixture was heated at 50°C for 10 min. Ether (50 mL) was added and the solution was washed with dilute hydrochloric acid (1 N, 10 mL), saturated sodium hydrogen carbonate (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm) with 97:3 hexane-ethyl acetate yielded crude **256** (0.1856 g, 56.3%). Only partial separation was possible by

centrifugal chromatography (Chromatotron, 4mm plate, Merck silica 60 PF_{254}) to yield **256** (0.100 g, 30.4%) as a homogeneous (TLC) yellow oil: IR (film) 1708, 1439, 739, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32 (m, 1H), 2.08 (m, 1H), 2.28 (m, 2H), 2.64 (m, 2H), 3.08 (bs, 1H), 3.64 (s, 2H), 5.58 (m, 1H), 5.62 (m, 1H), 7.18-7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.9, 31.8, 41.1, 44.3, 46.9, 126.9, 129.1, 129.8, 131.4, 133.8, 135.1, 204.7; exact mass, m/z 232.0921 (calcd for $C_{14}H_{16}OS$, m/z 232.0922).

3-(2-Cyclopenten-1-yl)-1-(phenylthio)propan-2-one 256 by reaction between lithium 2-lithio-2-(phenylthio)acetate and 255.

(Phenylthio)acetic acid[133] (0.150 g, 0.892 mmol) in THF (2 mL) was added dropwise over ca. 5 min to a stirred solution of LDA [made from diisopropylamine (0.28 mL, 2.00 mmol) and n-butyllithium (1.1 mL, 1.8 mmol)] in THF (10 mL) at -78°C. After 10 min the mixture was warmed to 0°C (ice bath) and stirred for a further 60 min. It was then cooled to -78°C and acid chloride **255** (0.140 g, 0.986 mmol) in THF (2 mL) was injected rapidly. Stirring was continued at -78°C for a further 20 min and then the solution was poured into a mixture of concentrated hydrochloric acid (0.35 g, 4.0 mmol) and ice (5 g) and partioned between diethyl ether (10 mL) and brine (10 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$) and evaporated. The residue was dissolved in dry benzene (10 mL) and the solution was

refluxed for 7 h. After evaporation of the solvent flash chromatography of the residue over silica gel (2 x 20 cm) with 90:10 hexane-ethyl acetate yielded **256** (0.064 g, 28.5%) as a yellow oil. It had spectral (^{1}H and ^{13}C NMR) and chromatographic (thin layer) properties identical to the authentic material prepared.

1-Methoxy-1-trimethylsiloxy-2-(2-cyclohexen-1-yl)ethene 260:

Ester **236** (0.970 g, 6.29 mmol) in THF (2 mL) was added dropwise over ca. 15 min to LDA [made from diisopropylamine (1.2 mL, 8.6 mmol) and n-butyllithium (4.6 mL, 1.5 M in hexanes, 6.9 mmol)] in THF (20 ml) at -78°C. After 20 min chlorotrimethylsilane (0.96 mL, 7.56 mmol) was injected rapidly. After 5 min the cooling bath was removed and the mixture was allowed to warm to room temperature over 30 min. The solution was evaporated and kugelrohr distillation of the residue (105-110°C, 15 mm) yielded **260** (1.20 g, 84.3%) as a clear colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 9H), 1.24 (m, 1H), 1.50 (m, 1H), 1.62 (m, 1H), 1.74 (m, 1H), 1.90 (bs, 2H), 2.94 (m, 1H), 3.46 (s, 3H), 3.56 (d, 1H), 5.46 (m, 1H), 5.58 (m, 1H). The silyl ketene acetal was used in subsequent experiments without further purification. The purity was checked (^{1}H NMR, 400 MHz) periodically; however, no significant decomposition was apparent during prolonged storage under dry conditions.

Methyl 2-(2-cyclohexen-1-yl)-3-oxobutanoate (a mixture of isomers) 262:

Silyl ketene acetal **260** (0.1624 g, 0.717 mmol) in dichloromethane (5 mL) was added dropwise over 1 h to a stirred solution of freshly distilled acetyl chloride (0.10 mL, 1.4 mmol) and anhydrous zinc chloride (0.020 g, 0.15 mmol) in dichloromethane (5 mL) at room temperature. Stirring was continued for a further 1 h and the mixture was then poured into saturated sodium hydrogen carbonate (15 mL) and extracted with diethyl ether (2 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm) with 88:12 hexane-ethyl acetate yielded two fractions F1 (0.022g) and **262** (F2) (0.0615 g, 43.7%; a 1:1 mixture of two isomers) as a TLC pure clear colorless liquids: The ^1H NMR spectrum of the first fraction was identical to that of **236**. Compound **262** had: IR (hexane cast) 1744, 1718, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (data for both isomers) δ 1.30 (m, 2H), 1.58 (m, 2H), 1.76 (m, 4H), 2.00 (bs, 4H), 2.24 (s, 3H), 2.25 (s, 3H), 2.96 (bs, 2H), 3.38 (d, J = 7.5 Hz, 1H), 3.42 (d, J = 7.5 Hz, 1H), 3.73 (s, 3H), 3.74 (s, 3H), 5.42 (dd, J = 10, 2 Hz, 1H), 5.50 (dd, J = 10, 2 Hz, 1H), 5.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (data for both isomers) δ 20.9, 24.9, 25.0, 26.7, 29.4, 29.6, 35.2, 35.3, 52.1, 65.2, 65.2, 127.3, 127.6, 129.5, 129.8, 169.2, 169.3, 202.1, 202.3; exact mass, m/z 196.1095 (calcd for $C_{11}H_{16}O_3$, m/z 196.1099).

Methyl 4-chloro-2-(2-cyclohexen-1-yl)-3-oxobutanoate (a mixture of isomers) 264:

Freshly distilled chloroacetyl chloride (0.05 mL, 0.63 mmol) was added to a stirred solution of silyl ketene acetal **260** (0.141 g, 0.623 mmol) in THF (5 mL) at O°C. Triethylamine (0.09 mL, 0.65 mmol) was added with stirring and a white precipitate immediately formed. The ice bath was removed and the mixture was allowed to warm to room temperature. After a further 2 h a mixture of concentrated hydrochloric acid (0.090 g, 0.9 mmol), THF (2 mL) and water (3 mL) was added. After being stirred for 30 min the mixture was poured into saturated sodium hydrogen carbonate solution (15 mL) and extracted with diethyl ether (2 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm) with 90:10 hexane-ethyl acetate yielded two fractions F1 (0.0201g) as colorless liquid and **264** (F2) (0.0734 g, 51.1%; a 1:1 mixture of 2 isomers) as a clear pale yellow liquid: The ^1H NMR spectrum of the first fraction was identical to that of **236**: **264** had IR (CH_2Cl_2 cast) 1759, 1727, 1435, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (data for both isomers) δ 1.32 (m, 2H), 1.50-1.84 (m, 6H), 2.00 (bs, 4H), 3.00 (bs, 2H), 3.64-3.78 (m, 8H; including two s at 3.76, 6H), 4.26 (s, 2H), 4.28 (s, 2H), 5.38 (d, J = 10 Hz, 1H), 5.48 (d, J = 10 Hz, 1H), 5.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (data for both isomers) δ 20.8, 21.0, 25.0, 25.0, 26.8, 26.8, 35.5, 35.6, 48.3, 48.4, 52.5, 61.1, 61.4, 126.9, 127.2, 130.2, 130.4, 168.4, 196.3, 196.4 (one

resonance for OCH_3 and C=O) ; exact mass (isomer mixture), m/z 230.0711 (calcd for $C_{11}H_{15}ClO_3$, m/z 230.0710).

2-(Phenylthio)-1,1-bis-trimethylsilyloxy ethene 265:

n-Butyllithium (2.15 mL, 1.6 M in hexanes, 3.44 mmol) was added dropwise to a stirred solution of hexamethyldisilazane (0.79 mL, 3.74 mmol) in THF (60 mL) at -78°C. Stirring was continued for 20-30 min at 0°C and then the solution was cooled to -78°C. Ester **254** (0.747 g, 3.11 mmol) in THF (5 mL) was added dropwise over 5 min and after a further 20 min, chlorotrimethylsilane (0.51 mL, 4.0 mmol) was injected rapidly. The cooling bath was removed and the mixture allowed to warm to room temperature over ca. 30 min. The solvent was evaporated and petroleum ether (30 mL, bp. 30-60°C) was added to the residue. Insoluble materials were removed by filtration. Evaporation of the filtrate kugelrohr distillation (90°C, 0.1 mm) of the residue yielded a mixture of **265** along with **266** and **254** (total weight 0.7160 g; a ratio of **265**:**266**:**254** of 73:23:4, see discussion p 100). The mixture was used in subsequent experiments without further purification. IR (film) 1605, 1245, 1200, 848 cm^{-1}.

3-(2-cyclopenten-1-yl)-1-(phenylthio)propan-2-one 256 by the reaction of 265 and 255:

A solution of silylketene acetal **265** [0.856 g, as a mixture of **265** and **266** 76:24 (^{1}H NMR), 2.74 mmol] and acid chloride **255** (00765 g, 0.529 mmol) in dry chlorobenzene (5 mL) was refluxed for 16 h. The solvent was evaporated and then dioxane (10 mL) and dilute hydrochloric acid (0.25 mL, 0.25 mmol) were added. The solution was stirred at 50°C for 15 min. The majority of the dioxane was then evaporated and aqueous saturated sodium hydrogen carbonate (10 mL) was added. The solution was extracted with diethyl ether (2 x 20 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm) with 90:10 hexane-ethyl acetate yielded **256** (0.0543 g, 44.2%) as a yellow oil: It had spectral (^{1}H NMR) and chromatographic (thin layer) properties identical to the authentic material.

Methyl 4-bromo-2-(2-cyclopenten-1-yl)-3-hydroxybutanoate (a mixture of isomers) 267:

Ester **232** (0.200 g, 1.43 mmol) in THF (1.5 mL) was added dropwise over 3 min to a stirred solution of LDA [from diisopropylamine (0, 22mL, 1.6 mmol) and n-butyllithium (0.93 mL, 1.6 M in hexanes, 1.5 mmol)] in THF (5 mL) at - 78°C. Stirring was continued for 30 min and then a solution of bromoacetaldehyde in

dichloromethane (1.4 mL, 1.4 mmol of bromoacetaldehyde) was added rapidly. After 5 min the reaction was quenched by addition of glacial acetic acid (0.30 g, 5.0 mmol) in THF (2mL). The cold bath was removed and the mixture was allowed to warm to room temperature. Water (10 mL) was added and the solution was extracted with diethyl ether (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm) with 85:15 hexane-ethyl acetate yielded **267** (0.256 g, 68%; as a mixture of 4 diastereoisomers, 2 major isomers and 2 minor isomers) as a yellow oil: IR ($CHCl_3$ cast) 3480, 1729, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (approximate intergrals only) δ 1.62-1.78 (bm, 4H), 1.98-2.20 (bm, 4H), 2.26-2.46 (bm, 8H), 2.48-2.62 (m, 2H), 2.76 (m, 6H), 3.20 (bs, 4H), 3.50-3.80 [bm, 20H; including s at 3.68 (major isomer), 3.70 (major isomer), 3.74 (minor isomer) and 3.76 (minor isomer)], 4.00-4.16 (bm, 4H), 5.54-5.90 (bm, 8H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.6, 27.3, 28.4 and 28.6 ($C_{5'}$); 31.7, 31.8 and 32.0 ($C_{4'}$); 36.1, 36.4, 37.9 and 38.4 ($C_{1'}$); 44.8, 45.2, 45.3 and 45.7 (C_4); 51.5, 51.6, 51.7 and 51.7 (OCH_3); 52.7, 52.9, 54.0 and 54.6 (C_2); 70.9, 71.0, 71.1 and 71.3 (C_3); 131.4, 131.5, 132.0, 132.4, 132.5, 132.8 and 132.8 ($C_{2'}$ and $C_{3'}$); 173.2, 173.3, 174.2 and 174.5 (C=O) (2 peaks absent, one methylene and one olefinic); mass (14 eV, 100°C), 264, 231, 198, 180, 165, 139, 67. Anal. Calcd for $C_{10}H_{15}O_3Br$: C, 45.65; H, 5.75; O, 18.24. Found (for total reaction product): C, 45.42; H, 5.70; O, 18.52.

Methyl 2-(2-cyclopenten-1-yl)-3-oxo-4-(phenylseleno)butanoate (a mixture of isomers) 270:

A solution of **233** (0.184 g, 542 mmol) in dichloromethane (2 mL) was added dropwise to a cooled (-20.° C) suspension, prepared by stirring dimethyl sulfide (0.085 mL, 1.16 mmol) and N-chlorosuccinimide (0.110 g, 0.824 mmol) in dichloromethane (3 mL) at 0 °C for 0.5 h. The solution was stirred at -20 °C for 3 h and then triethylamine (0.11 mL, 0.79 mmol) was added in one portion. After 5 min the mixture was warmed rapidly to ca. 5 °C and partitioned between water (10 mL) and diethyl ether (25 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (10 mL). The organic layers were combined, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 90:10 hexane-ethyl acetate yielded **270** (0.137 g, 75.1%; a 1:1 mixture of two diastereoisomers) as a TLC pure yellow oil: IR (hexane cast) 1743, 1706, 1438, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (data for both isomers) δ 1.48 (m, 2H), 2.06 (m, 2H), 2.32 (m, 4H), 3.40 (m, 2H), 3.62-3.80 (m, 12H, including two s centered at 3.69), 5.46 (m, 1H), 5.62 (m, 1H), 5.80 (m, 2H), 7.28 (m, 6H), 7.50 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHZ) (data for both isomers) δ 27.8, 28.0, 31.6, 31.7, 35.7, 35.9, 45.1, 45.5, 52.1, 62.0, 62.2, 127.9, 128.8, 129.2, 131.5, 132.8, 132.9, 133.2, 133.4, 169.1, 169.2, 198.6, 198.7 (only one resonance for OCH_3); exact mass (isomer mixture), m/z 338.0424 (calcd for $C_{16}H_{18}O_3Se$, m/z 338.0421). Anal. Calcd for $C_{16}H_{18}O_3Se$: C, 56.98; H, 5.38; O, 14.23. Found (isomer mixture): C, 57.27;

H, 5.44; O, 14.02.

Methyl 2-(2-cyclohexen-1-yl)-3-oxo-4-(phenylseleno) butanoate (a mixture of isomers) 272:

The procedure for the preparation of **270** was followed using **237** (0.1913 g, 0.541 mmol) in dichloromethane (2 mL), dimethyl sulfide (0.09 mL, 1.23 mmol) and N-chlorosuccinimide (0.110 g, 0.824 mmol) in dichloromethane (3 mL). After 3 h triethylamine (0.11 mL, 0.79 mmol) was added. After workup, flash chromatography of the residue over silica gel (3 x 20 cm) with 90:10 hexane-ethyl acetate yielded **272** (0.146 g, 76.8%; a 1:1 mixture of 2 diastereoisomers) as a TLC pure yellow oil: IR (hexane cast) 1743, 1707, 1438, 1163, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (data for both isomers) δ 1.23 (m, 2H), 1.48-1.76 (bm, 6H), 1.98 (bs, 4H), 2.94 (bs, 2H), 3.62-3.68 (m, 12H; including two s at 3.68 and 3.70), 5.36 (m, 1H), 5.44 (m, 1H), 5.74 (m, 2H), 7.28 (m, 6H), 7.50 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHZ) (data for both isomers) δ 20.8, 20.8, 25.0, 26.6, 26.7, 35.2, 35.5, 35.9, 36.2, 52.2, 62.0, 62.2, 127.5, 127.9, 128.8, 129.2, 129.5, 129.7, 133.2, 133.4, 168.9, 169.0, 198.3, 198.5 (one resonance for OCH_3, one methylene resonance coincident); exact mass (isomer mixture), m/z 352.0575 (calcd for $C_{17}H_{20}O_3Se$, m/z 352.0578). Anal. Calcd for $C_{17}H_{20}O_3Se$: C, 58.12; H, 5.74; O, 13.66. Found (isomer mixture): C, 58.15; H, 5.74; O, 13.64.

Methyl (3aα,6aα)-octahydro-2-oxopentalene-1-carboxylate 273:

The general procedure for radical cyclization (p.137) was followed using **270** (0.0882 g, 0.26 mmol) in benzene (10 mL), triphenylstannane [2 mL, 0.32 mmol from a solution of triphenylstannane 0.16 mL in benzene (4 mL)], AIBN (0.005 g, 0.03 mmol) in benzene (2 mL) and an addition period of 4 h. After a further 13 h the solvent was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm) with 90:10 hexane-ethyl acetate yielded **273** (0.038 g, 80.2%): IR ($CHCl_3$ cast) 1728, 1659, 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.80-2.40 (bm, 7H), 2.60-2.96 (bm, 2H), 3.08 (m, 1H), 3.30 (m, 0.5H), 3.80 and 3.82 (s, 3H), 11.42 (s, 0.5H)*; ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 25.3, 25.4, 32.6, 32.9, 33.3, 35.1, 36.4, 38.2, 39.9, 44.6, 44.6, 45.2, 51.0, 52.5, 61.0, 170.0, 175.3 (resonance for C=O absent, only one resonance for C_1 observed); exact mass, m/z 182.0940 (calcd for $C_{10}H_{14}O_3$, m/z 182.0943). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 66.06; H, 7.81. * NMR indicates ca. 50% of the enol tautomer is present.

Methyl (3aα,7aα)-octahydro-2-oxo-2H-indene-1-carboxylate 274:

The general procedure for radical cyclization (p.137) was followed using **272** (0.1266 g, 0.36 mmol) in benzene (10 mL), triphenylstannane (0.12 mL, 0.47 mmol) in benzene (5 mL), AIBN (0.010 g, 0.06 mmol) in benzene (5 mL) and an addition

period of 8.5 h. After a further 8.5 h the solvent was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm) with 90:10 hexane-ethyl acetate yielded two fractions **262** (0.0065 g, 9.2%) and **274** (0.0491 g, 69.5%) as colorless oils: The ^{1}H NMR spectrum of the first fraction was identical to that of **262**: **274** had IR (hexane cast) 1756, 1727, 1436, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (m, 1H), 1.32 (m, 1H), 1.46-1.70 (m, 6H), 2.14 (dd, AB of ABX, J_{AB} = 18 Hz, 1H), 2.34 (bs, 1H), 2.46 (dd, AB of ABX, J_{AB} = 18 Hz, 1H), 2.74 (se, J = 5 Hz, 1H), 3.22 (d, J = 10.5 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.0, 23.9, 26.4, 28.4, 34.0, 40.0, 45.4, 52.2, 56.5, 169.9, 211.7, minor peaks at 19.8, 24.2, 24.6, 33.8, 38.8, 39.9, 61.3; exact mass, m/z 196.1096 (calcd for $C_{11}H_{16}O_3$, m/z 196.1099). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.38; H, 8.13.

(Phenylseleno)-2-cyclopenten-1-yl acetate 275:

Pyridine (0.4 mL, 4.9 mmol) was added to a stirred solution of **255** (0.4940 g, 3.42 mmol) in THF (12 mL) at 0°C. After stirring for 10 min a solution of benzeneselenol (0.660 g, 4.20 mmol) in benzene (12 mL) was injected over ca. 5 min. The ice bath was removed and the mixture was allowed to reach room temperature. After a further 75 min, diethyl ether (25 mL) and Celite (1g) were added. The mixture was filtered and the filtrate was washed with brine (20 mL), dried ($MgSO_4$) and

evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm) with 99.5:0.5 hexane-ethyl acetate yielded **275** (0.8115 g, 89.5%) as a yellow oil: IR (film) 1725, 1439, 738, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.54 (m, 1H), 2.14 (m, 1H), 2.36 (m, 2H), 2.74 (m, 2H), 3.18 (bs, 1H), 5.68 (m, 1H), 5.78 (m, 1H), 7.36 (m, 3H), 7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.5, 31.8, 42.4, 53.3, 126.8, 128.7, 129.0, 131.3, 133.1, 135.7, 199.1; exact mass, m/z 266.0210 (calcd for $C_{13}H_{14}OSe$, m/z 266.0210). Anal. Calcd for $C_{13}H_{14}OSe$: C, 58.87; H, 5.32; O, 6.03. Found: C, 58.97; H, 5.28; O, 6.33.

3-(2-cyclopenten-1-yl)-1-(phenylseleno)propan-2-one 276:

Dry ethereal diazomethane (5 mL, 0.25 M) was added to a stirred mixture of **275** (0.4027 g, 1.52 mmol) and copper(I)iodide (0.050 g, 0.08 mmol) at room temperature. More diazomethane (total of 17.5 mL of the solution) was added at 30 min intervals until no starting material could be detected (TLC). The addition took 3.5 h. Silica gel (0.5g) was added and the mixture was stirred for 5 min, filtered and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm) with 96:4 hexane-ethyl acetate yielded **276** (0.1790 g, 42.2%) as a pale yellow oil: IR ($CHCl_3$ cast) 1710, 1439, 738, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35 (m, 1H), 2.10 (m, 1H), 2.38 (m, 2H), 2.72 (m, 2H), 3.08 (m, 1H), 3.58 (s, 2H), 5.60 (m, 1H), 5.75 (m, 1H), 7.38 (m, 3H), 7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.9,

31.8, 36.4, 41.3, 47.1, 127.9, 129.3, 131.3, 133.4, 133.9, 204.9, (1 peak absent from SeC_6H_5); exact mass, m/z 280.0370 (calcd for $C_{14}H_{16}OSe$, m/z 280.0366). Anal. Calcd for $C_{14}H_{16}OSe$: C, 60.22; H, 5.78; O, 5.73. Found: C, 60.29; H, 5.84; O, 6.00.

1-Chloro-1-(phenylseleno)-2-heptanone 283:

n-Hexanoyl chloride (0.23 mL, 1.5 mmol) was injected dropwise with intermittent agitation into an ethereal solution of diazomethane (20 mL, 4.4 mmol) in a 50 mL round bottomed flask sealed with a rubber septum. The mixture was kept at 3°C for 17 h with protection from light. The solution was then warmed to room temperature (to remove excess diazomethane), dried ($CaSO_4$) and evaporated to yield the crude diazoketone **280** (0.220 g) as a homogeneous (TLC) yellow oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 (t, 3H), 1.50 (m, 4H), 1.82 (m, 2H), 2.50 (m, 2H), 5.40 (bs, 1H).

Phenylselenenyl chloride (0.287 g, 1.50 mmol) in dichloromethane (1 mL) was added dropwise to a stirred solution of the crude diazoketone **280** (0.205g) in dichloromethane (5 mL). Rapid decolorization took place with the evolution of nitrogen. The mixture was partioned between brine (10 mL) and diethyl ether (50 mL) and the organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm) with 97:3 and then 94:6 hexane-ethyl acetate

yielded **283** (0.36 g, 85%) as a clear yellow oil: IR (hexane cast) 1720, 1439, 739, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 7 Hz, 3H), 1.28 (m, 4H), 1.58 (m, 2H), 2.56 (ddd, J = 17, 7, 1 Hz, 1H), 2.78 (ddd, J = 17, 7, 1 Hz, 1H), 5.54 (s, 1H), 7.36 (m, 3H), 7.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 13.9, 23.4, 23.8, 31.2, 37.9, 60.8, 129.5, 129.7, 135.9, 199.7, (1 peak absent from SeC_6H_5); exact mass, m/z 304.0137 (calcd for $C_{13}H_{17}ClOSe$, m/z 304.0133). Anal. Calcd for $C_{13}H_{17}ClOSe$: C, 51.41; H, 5.64; O, 5.27. Found: C, 51.71; H, 5.57; O, 5.63.

General Procedure for the Preparation of (2-Cycloalken-1-yl)propan-2-ones.

Oxalyl chloride (1.25 equiv.) was added dropwise to a stirred solution of the 2-cycloalkenen-1-yl acetic acid (1 equiv.) in benzene at 0°C. The mixture was stirred for 10-15 min before the ice bath was removed and the reaction allowed to warm to room temperature. After a further 2-3 h the benzene was evaporated. Distillation of the residue under reduced pressure (water aspirator; protection from moisture) yielded the acid chloride which was either used directly or stored (at ca. 0°C).

Methyllithium (MeLi) [6 equiv., in diethyl ether (Aldrich)] was added dropwise to a stirred suspension of copper(I)iodide (3 equiv.) in diethyl ether at ca. - 35°C. Initially a yellow suspension formed (MeCu) which, upon addition of the second equivalent of methyllithium, disappeared, resulting in a clear colorless solution of

lithium dimethyl cuprate. The dry-ice 2-propanone bath was allowed to warm to -15°C over ca. 25 min and was then cooled to - 78°C. Freshly distilled acid chloride (1 equiv.) in diethyl ether was injected rapidly into the vigorously stirred solution. Stirring was continued at - 78°C for a further 20 min Then anhydrous methanol (ca. 10 equiv.) was injected in one portion. After 5-10 min the cooling bath was removed and the solution allowed to warm to room temperature. The precipitate was filtered off [the addition of Celite (1-2g) prior to filtration was helpful] and washed with diethyl ether (5 x 10 mL portions). The filtrate was shaken with brine (10 mL) and the organic layer was dried ($MgSO_4$) and evaporated. Kugelrohr distillation of the residue under reduced pressure (water aspirator; protection from moisture) yielded the methyl ketone.

1-(2-cyclopenten-1-yl)propan-2-one 277:

The general procedure was followed using acid chloride **255** (1.1794 g, 8.16 mmol) in diethyl ether (5 mL), lithium dimethyl cuprate [made from MeLi (35.0 mL, 1.17 M in diethyl ether, 41 mmol) and copper(I)iodide (4.70 g, 24.7 mmol)] in diethyl ether (15 mL) and methanol (3 mL, 74 mmol). After workup, the solvent was evaporated at atmospheric pressure and Kugelrohr distillation of the residue yielded **277** [0.890 g, 96% pure (VPC OV-I, 150°C), 84.3%] as a colorless liquid: bp 40°C, 15 mm; IR (film) 2937, 1712, 1361, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36 (m, 1H), 2.04-2.16 (m, 4H; including s at 2.12), 2.20-2.52 (m, 4H), 3.10 (bs, 1H),

5.58 (m, 1H), 5.70 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.8, 30.2, 31.8, 41.1, 50.0, 131.3, 134.0, 208.3; exact mass, m/z 124.0889 (calcd for $C_8H_{12}O$, m/z 124.0888).

1-(2-cyclohexen-1-yl)propan-2-one 284:

The general procedure was followed using acid chloride **257** (1.1533 g, 7.27 mmol) in diethyl ether (5 mL), lithium dimethyl cuprate [made from MeLi (31.5 mL, 1.17 M in diethyl ether, 37 mmol) and copper(I)iodide (3.75 g, 19.7 mmol)] in diethyl ether (15 mL) and methanol (2.9 mL, 72 mmol). After workup the solvent was evaporated and Kugelrohr distillation of the residue yielded **284** [0.840 g, 94% pure (VPC OV-I, 150°C), 78.6%] as a colorless liquid: bp 83-85°C, 22 mm; IR (hexane cast) 2924, 1717, 1360, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (m, 1H), 1.56 (m, 1H), 1.66 (m, 1H), 1.78 (m, 1H), 1.96 (bs, 2H), 2.12 (s, 3H), 2.40 (m, 2H), 2.62 (bs, 1H), 5.50 (m, 1H), 5.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.2, 25.1, 29.0, 30.4, 31.3, 50.1, 127.9, 130.5, 207.8; exact mass, m/z 138.1040 (calcd for $C_9H_{14}O$, m/z 138.1045).

1-(2-cyclohepten-1-yl)propan-2-one 286:

The general procedure was followed using oxalyl chloride (0.40 mL, 4.6 mmol) and acid **285**[153] (0.5279 g, 3.42 mmol) in benzene (10 mL). Evaporation of

the benzene under reduced pressure and kugelrohr distillation of the residue yielded the acid chloride which was used directly: bp (110°C, 15 mm).

The acid chloride in diethyl ether (5 mL) was added to lithium dimethyl cuprate [made from MeLi (15.0 mL, 1.17 M in diethyl ether, 18 mmol) and copper(I)iodide (1.65 g, 8.7 mmol)] in diethyl ether (15 mL). The reaction was quenched with methanol (1.2 mL, 30 mmol). After workup the solvent was evaporated under reduced pressure and kugelrohr distillation of the residue yielded **286** [0.3992 g, >99% pure (VPC OV-I 170°C), 76.7%] as a clear liquid: bp 95°C, 15 mm; IR (hexane cast) 2919, 1718, 1360 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (m, 2H), 1.50-1.70 (bm, 3H), 1.86 (m, 1H), 2.04 (m, 5H; including s at 2.10), 2.46 (m, 2H), 2.74 (bs, 1H), 5.40 (m, 1H), 5.74 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.9, 28.8, 30.0, 30.2, 33.5, 35.8, 50.8, 131.9, 136.1, 207.9; exact mass, m/z 152.1201 (calcd for $C_{10}H_{16}O$, m/z 152.1201).

Endo- and Exo-6-bicyclo(2.2.2.)octen-2-yl methyl ketone 288 (a mixture of isomers):

The general procedure was followed using oxalyl chloride (0.25 mL, 2.9 mmol) and acid **287**[154] [0.320 g, 93:7 endo:exo (^1H NMR 400 MHz), 2.10 mmol] in benzene (10 mL). Evaporation of the benzene and kugelrohr distillation of the residue yielded the acid chloride which was used directly: bp 110°C, 15 mm.

The acid chloride in diethyl ether (5 mL) was added to lithium dimethyl cuprate [made from MeLi (9.0 mL, 1.17 M in diethyl ether, 15 mmol) and copper(I)iodide (1.00 g, 5.3 mmol)] in diethyl ether (10 mL). The reaction was quenched with methanol (0.75 mL, 18 mmol). After workup the solvent was evaporated and kugelrohr distillation of the residue yielded **288** [0.282 g, 89.4%: VPC analysis gives exo:endo 7.3:92.7; exo isomer eluted (1.82 min) endo at (1.97 min) (OV-I 180°C)] as a moderately viscous yellow oil: bp 80°C, 15 mm; IR (hexane cast) 2942, 1710, 1360, 1170, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) endo-isomer δ 1.10-1.34 (m, 2H), 1.40-1.80 (m, 4H), 2.10 (s, 3H), 2.40-2.70 (m, 2H), 2.86 (s, 1H), 5.08 (ddd, J = 7, 7, 1 Hz, 1H), 5.26 (ddd, J = 7, 7, 1 Hz, 1H), peaks for exo isomer at 2.16 (s), 2.80 (bs); ^{13}C NMR ($CDCl_3$, 100.6 MHz) endo-isomer δ 24.6, 26.0, 28.1, 28.9, 29.8, 32.2, 51.7, 131.2, 135.2, 209.3, peaks for exo isomer at 20.9, 25.1, 27.7, 32.1, 51.3, 133.9, 135.5; exact mass (isomer mixture), m/z 150.1047 (calcd for $C_{10}H_{14}O$, m/z 150.1045).

4-Methyl-5-hexen-2-one 290:

The general procedure was followed using oxalyl chloride (0.9 mL, 10 mmol) and acid **289**[155] (0.946 g, 8.25 mmol) in benzene (15 mL). Evaporation of the benzene at atmospheric pressure and kugelrohr distillation of the residue gave the acid chloride [0.684 g, 72.5% pure (^1H NMR 400 MHz) contaminated with benzene]

which was used as such: bp 60°C, 40 mm.

The acid chloride in diethyl ether (5 mL) was added to lithium dimethyl cuprate [made from MeLi (25.0 mL, 1.17 M in diethyl ether, 29 mmol) and copper(I)iodide (2.95 g, 15.5 mmol)] in diethyl ether (10 mL). The reaction was quenched with methanol (2.0 mL, 49 mmol). After workup the solvent was evaporated at atmospheric pressure and kugelrohr distillation of the residue yielded **290** [0.430 g, 90% pure (^{1}H NMR 400 MHz), contaminated with benzene, 42%] as a clear colorless liquid: bp 125°C, 700 mm; IR ($CDCl_3$ cast) 2920, 1720, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (d, J = 7 Hz, 3H), 2.12 (s, 3H), 2.36 and 2.46 (AB of ABX, J_{AB} = 16 Hz, 2H), 2.70 (m, 1H), 4.94 (dt, J = 10.5, 1.5 Hz, 1H), 5.00 (dt, J = 16.75, 1.5 Hz, 1H), 5.76 (ddd, J = 16.75, 10.5, 7.0 Hz, 1H), 2.48; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.8, 30.4, 33.5, 50.5, 113.1, 128.4, 143.0, 207.5.

General procedure for Preparation of α-(Phenylseleno)methyl Ketones

The ketone (1 equiv.) in THF was added dropwise over ca. 5 min to a stirred solution of LDA (1.05-1.1equiv.) [made from disopropylamine (1.1-1.2 equiv.) and n-butyllithium (1.05-1.1 equiv.)] in THF at -78 °C. After a further 10 min phenylselenenyl chloride (1.25 equiv.) in THF was injected rapidly. The solution was stirred at -78°C for a further 5-10 min at which point saturated aqueous ammonium chloride (2 mL) was added. The mixture was allowed to warm to room temperature

(ca. 20 min) and brine was added. The organic layer was separated and the aqueous layer was extracted once with diethyl ether. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel as described for the individual experiments yielded the pure α-(phenylseleno)methyl ketones.

3-(2-cyclopenten-1-yl)-1-(phenylseleno)propan-2-one 276:

The general procedure was followed using **277** [0.100 g, 96% purity (VPC), 0.77 mmol] in THF (2 mL), LDA [made from diisopropylamine (0.125 mL, 0.89 mmol) and n-butyllithium (0.55 mL, 1.6 M in hexanes, 0.88 mmol)] in THF (5 mL) and phenylselenenyl chloride (0.180 g, 0.94 mmol) in THF (0.5 mL). After workup flash chromatography of the residue over silica gel (2 x 20 cm) with 96:4 hexane-ethyl acetate yielded **276** (0.149 g, 69.3%) as a yellow oil: It had spectral (^1H NMR and ^{13}C NMR) and chromatographic (TLC) properties identical to an authentic sample.

3-(2-cyclohexen-1-yl)-1-(phenylseleno)propan-2-one 291:

The general procedure was followed using **284** [0.205 g, 94% purity (VPC), 1.39 mmol] in THF (2 mL), LDA [made from diisopropylamine (0.24 mL, 1.7 mmol) and n-butyllithium (1.1 mL, 1.5 M in hexanes, 1.65 mmol)] in THF (10 mL) and phenylselenenyl chloride (0.350 g, 1.83 mmol) in THF (1 mL). After workup flash

chromatography of the residue over silica gel (2 x 20 cm) with 96:4 hexane-ethyl acetate yielded **291** (0.295 g, 72.4%) as a yellow oil: IR (hexane cast) 1710, 1440, 738, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (m, 1H), 1.44-1.80 (bm, 3H), 1.98 (bs, 2H), 2.56-2.70 (bm, 3H), 3.58 (s, 2H), 5.44 (m, 1H), 5.66 (m, 1H), 7.26 (m, 3H), 7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 21.0, 25.1, 28.8, 31.2, 36.4, 47.0, 127.9, 128.8, 128.9, 129.3, 130.4, 133.3, 204.8; exact mass, m/z 294.0527 (calcd for $C_{15}H_{18}OSe$, m/z 294.0523). Anal. Calcd for $C_{15}H_{18}OSe$: C, 61.43; H, 6.19; O, 5.46. Found: C, 61.48; H, 6.19; O, 5.61.

3-(2-Cyclohepten-1-yl)-1-(phenylseleno)propan-2-one 292:

The general procedure was followed using **286** (0.125 g, 0.821 mmol) in THF (2 mL), LDA [made from diisopropylamine (1.4 mL, 1.0 mmol) and n-butyllithium (0.65 mL, 1.5 M in hexanes, 0.98 mmol)] in THF (10 mL) and phenylselenenyl chloride (0.200 g, 1.04 mmol) in THF (1 mL). After workup flash chromatography of the residue over silica gel (3 x 20 cm) with 94:6 hexane-ethyl acetate yielded **292** (0.190 g, 75.3%) as a yellow oil: IR (hexane cast) 1703, 1438, 737, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38 (m, 2H), 1.48-1.70 (bm, 3H), 1.86 (m, 1H), 2.10 (m, 2H), 2.56-2.84 (bm, 3H; including bs at 2.74, 1H), 3.68 (s, 2H), 5.40 (m, 1H), 5.74 (m, 1H), 7.28 (m, 3H), 7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 26.8, 28.7, 30.1, 33.4, 35.5, 36.3, 47.7, 127.9, 129.3, 132.0, 133.3, 136.1, 204.8, (1

peak absent from SeC_6H_5); exact mass, m/z 308.0684 (calcd for $C_{16}H_{20}OSe$, m/z 308.0679). Anal. Calcd for $C_{16}H_{20}OSe$: C, 62.54; H, 6.56; O, 5.21. Found: C, 62.77; H, 6.56; O, 5.50.

Endo-2-Bicyclo(2.2.2)octen-5-yl (phenylseleno)methyl ketone 293:

The general procedure was followed using **288** [0.230 g, 92.7% endo, 1.48 mmol] in THF (2 mL), LDA [made from diisopropylamine (0.26 mL, 1.9 mmol) and n-butyllithium (1.05 mL, 1.5 M in hexanes, 1.6 mmol)] in THF (10 mL) and phenylselenenyl chloride (0.365 g, 1.91 mmol) in THF (0.5 mL). After workup flash chromatography of the residue over silica gel (3 x 20 cm) with 96:4 hexane-ethyl acetate yielded **293** (0.293 g, 64.7%) as a yellow oil: IR (film) 1701, 1438, 738, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18 (m, 2H), 1.36-1.62 (m, 4H), 2.54 (bs, 1H), 2.76 (bs, 1H), 2.92 (ddd, J = 10, 7.5, 2 Hz, 1H), 3.62 (dd, AB J_{AB} = 12.5 Hz, 2H), 6.04 (ddd, J = 7, 7, 1 Hz, 1H), 6.24 (ddd, J = 7, 7, 1 Hz, 1H), 7.26 (m, 3H), 7.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.3, 25.9, 29.3, 29.6, 32.4, 34.8, 48.8, 127.8, 129.2, 131.0, 133.3, 135.1, 206.6, (1 peak absent from SeC_6H_5); exact mass, m/z 306.0530 (calcd for $C_{16}H_{18}OSe$, m/z 306.0523). Anal. Calcd for $C_{16}H_{18}OSe$: C, 62.95; H, 5.94; O, 5.24. Found: C, 63.23; H, 5.89; O, 5.56.

4-Methyl-1-(phenylseleno)-5-hexen-2-one 294:

The general procedure was followed using **290** [0.200 g, 90% purity (^{1}H NMR), 1.60 mmol] in THF (2 mL), LDA [made from diisopropylamine (0.23 mL, 1.6 mmol) and n-butyllithium (1.0 mL, 1.5 M in hexanes, 1.5 mmol)] in THF (7 mL) and phenylselenenyl chloride (0.330 g, 1.72 mmol) in THF (1 mL). After workup flash chromatography of the residue over silica gel (3 x 20 cm) with 95:5 hexane-ethyl acetate yielded **294** (0.29 g, 68%) as a yellow oil: IR (hexane cast) 1704, 1438, 738, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (d, J = 6.5 Hz, 3H), 2.50-2.75 (bm, 3H), 3.60 (s, 2H), 4.92 (dt. J = 10, 1.5 Hz, 1H), 5.00 (dt, J = 17.5, 1.5, 1H), 5.70 (ddd, J = 17.5, 6.5, 10 Hz), 7.26 (m, 3H), 7.50 (m, 2H), peaks for **295** at 1.06(d), 1.25 (d), 2.24 (s) and 2.20 (s); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.7, 33.4, 36.5, 47.5, 113.1, 127.8, 129.1, 129.3, 133.3, 142.7, 204.1; exact mass, m/z 268.0362 (calcd for $C_{13}H_{16}OSe$, m/z 268.0366). Anal. Calcd for $C_{13}H_{16}OSe$: C, 58.43; H, 6.03; O, 5.99. Found: C, 58.45; H, 5.91; O, 6.06.

Cyclization of α-(Phenylseleno)methyl ketones.

(3aα,6aα)-Octahydro-2H-pentalen-2-one 278:

The general procedure for radical cyclization (p.137) was followed using **276** (0.1279 g, 0.458 mmol) in benzene (20 mL), triphenylstannane (0.195 g, 0.556 mmol) in benzene (10 mL) and AIBN (0.012 g, 0.07 mmol) in benzene (10 mL) and an

addition period of 13.5 h. After a further 1.5 h the solvent was evaporated. Analysis by VPC (OV-1 150°C) showed a ratio of the presence of **278** and **288** in a ratio of 78.8:21.2. Flash chromatography of the residue over silica gel (2 x 20 cm) with 95:5 hexane-ethyl acetate yielded two fractions **277** (0.003 g, 5.3%) and **278** (0.0369 g, 64.9%) as colorless liquids: The ^{1}H NMR spectrum (400 MHz) of the first fraction was identical to that of **277**: **278** had IR (film) 2951, 1741, 1400, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (m, 2H), 1.64 (m, 1H), 1.72 (m, 1H), 1.98 (m, 2H), 1.98-2.50 (AB of ABX centered at 2.25 J_{AB} = 20 Hz, 4H), 2.68 (bs, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 25.6, 33.5, 39.7, 44.7, 220.8; exact mass, m/z 124.0890 (calcd for $C_8H_{12}O$, m/z 124.0888).

(3aα,7aα)-octahydro-2H-inden-2-one 297:

The general procedure for radical cyclization (p.137) was followed using **291** (0.116 g, 0.400 mmol) in benzene (20 mL), triphenylstannane (0.12 mL, 0.47 mmol) in benzene (10 mL) and AIBN (0.015 g, 0.09 mmol) in benzene (10 mL) and an addition period of 17 h. After a further 2 h the solvent was evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm) with 95:5 hexane-ethyl acetate yielded two fractions **284** (0.0064 g, 11.6%) and **297** (0.0395 g, 71.4%) as colorless liquids: The ^{1}H NMR spectrum (400 MHz) of the first fraction was identical to that of **284**: **297** had IR (hexane cast) 2925, 1744, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$,

400 MHz) δ 1.30-1.64 (bm, 8H), 2.26 (m, 4H), 2.30 (bs, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.5, 27.5, 35.6, 43.3, 219.7; exact mass, m/z 138.1047 (calcd for $C_9H_{14}O$, m/z 138.1045).

(3aα,8aα) and (3aα,8aβ)-decahydro-2H-Azulen-2-one (a mixture of isomers) 298:

The general procedure for radical cyclization (p.137) was followed using **292** (0.148 g, 0.482 mmol) in benzene (20 mL), triphenylstannane (0.15 mL, 0.59 mmol) in benzene (10 mL) and AIBN (0.0140 g, 0.09 mmol) in benzene (10 mL) and an addition period of 13.5 h. After a further 1.5 h the solvent was evaporated and VPC analysis (OV-I 180°C) of the crude reaction mixture showed the presence of **286** and **298** in a ratio of 89:21. Flash chromatography of the residue over silica gel (2 x 20 cm) with 95:5 and then 90:10 hexane-ethyl acetate yielded two fractions **286** (0.0116 g, 15.8%) and **298** (0.053 g, 73.0%) as colorless liquids: The ^1H NMR spectrum (400 MHz) of the first fraction was identical to that of **286**: cis- and trans-**298** and **299** had IR (hexane cast) 2923, 1744, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (approximate inetgrals only) δ 1.20-2.04 (bm, 13H), 2.42 (m, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ cis-and trans-**298** 26.7, 27.2, 27.9, 31.4, 32.4, 34.5, 39.8, 43.5, 46.4, 48.0, 218.5, 219.6, peaks for **299** at 26.0, 34.7, 35.2, 48.4; exact mass

(isomer mixture), m/z 152.1204 (calcd for $C_{10}H_{16}O$, m/z 152.1201).

Tricyclo(4.3.1.$0^{3,7}$)decan-5-one (5-Isotwistanone) 300:

The general procedure for radical cyclization (p.137) was followed using **293** (0.130 g, 0.426 mmol) in benzene (20 mL), triphenylstannane (0.182 g, 0.518 mmol) in benzene (10 mL) and AIBN (0.0130 g, 0.08 mmol) in benzene (10 mL) and an addition period of 13.5 h. After a further 1.5 h the solvent was evaporated and flash chromatography of the residue over silica gel (2 x 30 cm) with 96:4 hexane-ethyl acetate yielded **300** (0.0554 g, 86.6%) as a white solid. Compound **300** could not be visualized (TLC) with our methods of development and the fractions were analyzed by VPC (OV-I 200°C): mp 108-113°C (lit.[174] mp 115-118°C); IR (hexane cast) 2932, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (dm, J = 14 Hz, 1H), 1.50 (m, 3H), 1.64 (bs, 1H), 1.68-2.00 (bm, 5H), 2.02-2.30 (m, 3H including AB of ABX J_{AB}= 18 Hz, 2H), 2.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.2, 24.2, 26.3, 30.2, 32.6, 33.8, 35.1, 46.5, 48.4, 222.5; exact mass, m/z 150.1045 (calcd for $C_{10}H_{14}O$, m/z 150.1045).

3-Methylcyclohexanone 301:

The general procedure for radical cyclization (p.137) was followed using **294** (0.1387 g, 0.519 mmol) in benzene (20 mL), triphenylstannane (0.15 mL, 0.59 mmol)

in benzene (10 mL) and AIBN (0.013 g, 0.08 mmol) in benzene (10 mL) and an addition period of 13.5 h. After a further 2.5 h the majority of the benzene was evaporated at atmospheric pressure. The residue was placed in a volumetric flask (5 mL) and made up with benzene. The yield of 3-methylcyclohexanone **301** was determined by VPC analysis (OV-I, 140°C). A calibration graph was determined with 6 standard solutions of 3-methylcyclohexanone (Aldrich) in benzene (5 mL each) and the yield was calculated as 0.044 ± 0.001g (75.6 ± 1.7%). The benzene was evaporated and the residue added to a 2,4-dinitro phenylhydrazone solution in phosphoric acid (5 mL, 1.25 mmol). \The solution was stirred for 15 min, water (5 mL) was added and the mixture extracted with dichloromethane (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm) with 85:15 hexane-ethyl acetate yielded the 2,4-DNP derivative of 3-methylcyclohexanone (0.1263g 83%) The material was contaminated with ca. 10.5% of the derivative of **290**. An authentic sample of the derivative of commercial 3-methylcyclohexanone was prepared in a similar fashion.

Ethyl (E)-5-[(phenylseleno)methyl]tetrahydrofuran-2-ylideneacetate 307:[165]

N-(phenylseleno)pthalimide (0.555 g, 1.84 mmol) in dichloromethane (5 mL) at room temperature was added dropwise over 45 min to a stirred solution of β-keto

ester **308** (0.290 g, 1.70 mmol) and iodine (0.022 g, 0.087 mmol) in dichloromethane (3 mL). After a further 45 min the mixture was filtered. The filtrate was diluted with diethyl ether (50 mL), washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm) with 88:12 hexane-ethyl acetate yielded **307** (0.305 g, 55.0%) as a light yellow oil: IR (CH_2Cl_2 cast) 1702, 1644, 1372, 1115, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, J = 7 Hz, 3H), 1.82 (m, 1H), 2.24 (m, 1H), 2.96 (m, 2H), 3.20 (m, 1H), 3.24 (m, 1H), 4.08 (q, J = 7 Hz, 2H), 4.54 (qu, J = 6 Hz, 1H), 5.22 (s, 1H), 7.24 (m, 3H), 7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.5, 29.3, 30.3, 31.7, 59.2, 83.0, 90.1, 127.5, 129.2, 133.2, 168.4, 175.6, (1 peak absent from SeC_6H_5); exact mass, m/z 326.0432 (calcd for $C_{15}H_{18}O_3Se$, m/z 326.0421).

Ethyl (E)-5-methyltetrahydrofuran-2-ylideneacetate 309:

Solutions of triphenylstannane (0.135 g, 0.38 mmol) in benzene (10 mL) and AIBN (0.014 g, 0.08 mmol) in benzene (10 mL) were added simultaneously over a period of 13.5 h to a refluxing solution of **307** (0.105 g, 0.323 mmol) in benzene (20 mL). After a further 2.5 h the mixture was allowed to cool to room temperature and the benzene was then evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm) with 90:10 hexane-ethyl acetate yielded **309** (0.442 g, 80.4%) as a clear colorless liquid: IR (CH_2Cl_2 cast) 1706, 1643, 1113, 1050 cm^{-1}; ^1H NMR ($CDCl_3$,

400 MHz) δ 1.28 (t, J = 7 Hz, 3H), 1.38 (d, J = 6 Hz, 3H), 1.66 (m, 1H), 2.22 (m, 1H), 2.96 and 3.32 (dd, AB of ABX, J_{AB} = 12.5 Hz, 2H), 4.14 (q, J = 7 Hz, 2H), 4.52 (dqu, J = 8, 6 Hz, 1H), 5.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.5, 20.4, 30.8, 31.2, 59.1, 80.3, 89.5, 168.7, 176.3; exact mass, m/z 170.0944 (calcd for $C_9H_{14}O$, m/z 170.0943).

Methyl (E)-6-(phenylseleno)-5,6-dihydro-4H-pyran-2-ylacetate 310:

The literature procedure was followed[169] with the exception that the reaction time was extended from 2 h to 12 h. When the reaction was done using the recommended time (2 h) the product contained largely starting material. Chromatography several times over silica gel with 6:1 light petroleum ether (bp 35-60) diethyl ether yielded **310** as a pale yellow oil. The ^1H NMR spectrum showed that the presence of **312** (<5%) and this was removed under vacuum (10^{-3} mm) over a period of 24 h. The product was subjected again to flash chromatography before use in the following experiment. This purified material had: IR (film) 1742, 1152, 1022, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.70 (m, 1H), 1.90-2.10 (m, 3H), 3.00 (m, 3H; including dd, AB of ABX J_{AB} = 12.5 Hz, 1H and s at 3.02), 3.20 (dd, AB of ABX J_{AB} = 12.5 Hz, 1H), 3.70 (s, 3H), 4.04 (m, 1H), 4.64 (t, J = 4.0 Hz, 1H), 7.22 (m, 3H), 7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.8, 26.4, 31.8, 40.1, 51.9, 75.2, 98.9, 127.0, 129.1, 130.1, 132.8, 147.4, 170.7; exact mass, m/z

326.0421 (calcd for $C_{15}H_{18}O_3Se$, m/z 326.0421).

Methyl (E)-6-methyl-5,6-dihydro-4H-pyran-2-ylacetate 313:

The general procedure for radical cyclization (p.137) was followed using **310** (0.1391 g, 0.428 mmol) in benzene (20 mL), triphenylstannane (0.13 mL, 0.51 mmol) in benzene (10 mL), AIBN (0.0150 g, 0.09 mmol) in benzene (10 mL) and an addition period of 13.5 h. After a further 1.5 h the benzene was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm) with 95:5 hexane-ethyl acetate yielded two fractions **313** (F1) (0.0506 g, 69.5%)and F2 (0.0100 g, 13.7%): **313** had IR (film) 2920, 1747, 1260, 1150, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.26 (d, J = 6.5 Hz, 3H), 1.50-1.68 (m, 1H), 1.86-1.92 (m, 1H), 2.00-2.30 (m, 2H), 3.03 (s, 2H), 3.70 (s, 3H), 4.02 (m, 1H), 4.68 (m, 1H); exact mass, m/z 170.0944 (calcd for $C_9H_{14}O_3$, m/z 170.0943). The ^1H NMR spectrum (200 MHz) of second fraction was identical to that of **312**

Bicyclo(3.1.0.)hexan-2-one 316:

Alcohol **315** (1.1530 g, 11.75 mmol) in dichloromethane (5 mL) was added dropwise over ca. 5 min at room temperature to a stirred suspension of pyridinium dichromate (17.7 g, 47.0 mmol) and crushed 3 Á molecular sieves (3.1 g, Aldrich) in dichloromethane (5 mL). After 13 h no starting remained (TLC). The mixture was

diluted with diethyl ether (50 mL) and filtered through a silica gel pad (2 x 7 cm) which was washed with diethyl ether (4 x 50 mL). The filtrate was then washed with dilute hydrochloric acid (100 mL, 0.2 M), dried ($MgSO_4$) and evaporated at atmospheric pressure. Kugelrohr distillation of the residue yielded **316** (0.741 g, 65.6%) as a colorless liquid: bp 105°C, 15 mm; IR (film) 1727, 928 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.94 (m, 1H), 1.22 (m, 1H), 1.78 (m, 1H), 2.00-2.24 (bm, 5H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 13.3, 21.4, 22.5, 27.3, 31.2, 214.9; exact mass, m/z 96.0577 (calcd for C_6H_8O, m/z 96.0575).

3-[(Phenylseleno)methyl]cyclopentanone 314:

Iodotrimethylsilane (0.36 mL, 2.53 mmol) was added dropwise to a stirred solution of **316** (0.200 g, 2.08 mmol) in carbon tetrachloride (6 mL) at -20°C. After 30 min the solution was diluted with diethyl ether (50 mL), washed with saturated sodium sulfite solution (25 mL), dried ($MgSO_4$) and evaporated.

Sodium borohydride (0.055 g, 1.45 mmol) was added in portions to a stirred solution of diphenyl diselenide (0.490 g, 1.57 mmol) in punctilious ethanol (10 mL) at room temperature. After being stirred for 30 min the solution was cooled to 0°C in an ice bath.

The crude iodide, in ethanol (2 mL), was added dropwise to the stirred solution of sodium phenylselenate. The ice bath was removed after ca. 10 min and the mixure

allowed to warm to room temperature. After a further 4 h the mixture was partitioned between diethyl ether (50 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm) with 85:15 hexane-ethyl acetate yielded crude **317** (0.325 g, 61.5%) as a homogeneous (TLC) yellow oil. [Further purification by centrifugal chromatography (Chromatotron, 4mm plate Merck silica gel 60 PF_{254}) with 85:15 hexane-ethyl acetate proved unsuccessful]: IR (film) 1742, 1159, 738, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.62 (m, 1H), 1.94 (m, 1H), 2.10-2.52 (m, 5H), 3.02 (d, J = 7 Hz, 2H), 7.24 (m, 3H), 7.48 (m, 2H) minor peak at 3.28 (m); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.0, 33.4, 37.7, 38.4, 45.2, 127.2, 129.2, 130.1, 133.0, 217.5 minor peaks at 30.1, 39.3, 40.9, 45.8; exact mass (isomer mixture), m/z 254.0212 (calcd for $C_{12}H_{14}OSe$, m/z 254.0210).

Reaction of 314 with Triphenylstannane.

The general procedure for radical cyclization (p.137) was followed using **314** (0.1176 g, 0.464 mmol) in benzene (20 mL), triphenylstannane (0.192 g, 0.547 mmol) in benzene (10 mL) and AIBN (0.014 g, 0.085 mmol) in benzene (10 mL) and an addition period of 13.5 h. After a further 1.5 h the majority of the benzene was removed by distillation at atmospheric pressure using a 10 cm Vigreux column. The residue was dissolved in benzene, placed in a volumetric flask (5 mL) and made up

with benzene. The yield of 3-methylcyclopentanone was determined by VPC analysis (OV-I, 140°C). A calibration graph was determined with 5 standard solutions of 3-methylcyclopentanone (Aldrich) in benzene (5 mL each) and the yield was calculated as 0.038 ± 0.003g (84.1 ± 0.7%). GCMS analysis showed that the only major product was 3-methylcyclopentanone accompanied by a small amount (ca. 4%) of cyclohexanone.

1-(Phenylseleno)-6-hepten-2-ol 322:

5-Bromopentene (0.503 g, 3.37 mmol, Aldrich) in diethyl ether (2 mL) was added dropwise to a stirred suspension of magnesium metal (0.100 g, 4.11 mmol, 70-80 mesh) in diethyl ether (5 mL) at such a rate as to maintain gentle reflux. After the addition was complete the mixture was refluxed gently for a further 45 min. The mixture was then cooled to -30°C and freshly purified (phenylseleno)acetaldehyde (0.503 g, 2.56 mmol) was added dropwise over ca. 20 min while the temperature was maintained at -30°C. The mixture was then warmed gradually to room temperature (ca. 1 h) and stirred for a further 2 h at which point the excess of Grignard reagent was carefully destroyed by the dropwise addition of saturated aqueous ammonium chloride. The mixture was partitioned between diethyl ether (20 mL) and saturated ammonium chloride (10 mL). The aqueous layer was extracted with diethyl ether (2 x 20 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash

chromatography of the residue over silica gel (3 x 20 cm) with 90:10 hexane-ethyl acetate yielded **322** (0.427 g, 62.0%) as a yellow liquid. IR (hexane cast) 3400, 1478, 1438, 1023, 911, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.38-1.68 (bm, 4H), 2.04 (m, 2H), 2.42 (d, J = 4 Hz, 1H), 2.80-3.20 (m, AB of ABX J_{AB}=12.5 Hz centered at 3.02, 2H), 3.68 (bm, 1H), 4.90-5.08 (m, 2H), 5.78 (m, 1H), 7.24-7.36 (m, 3H), 7.48-7.60 (m, 2H); exact mass, m/z 270.0527 (calcd for $C_{13}H_{18}OSe$, m/z 270.0523).

1-(phenylseleno)-6-hepten-2-one 321:

The procedure for the preparation of **270** was followed using **322** (0.245 g, 0.910 mmol) in dichloromethane (1.5 mL), dimethyl sulfide (0.145 mL, 1.39 mmol) and N-chlorosuccinimide (0.186 g, 1.39 mmol) in dichloromethane (5 mL). After 6 h, triethylamine (0.21 mL, 1.5 mmol) was added. After workup, flash chromatography of the residue over silica gel (2 x 20 cm) with 6:1 light petroleum ether (bp 35-60 °C) diethyl ether yielded **321** (0.151 g, 62.1%) as a yellow oil: IR (film) 1709, 1440, 737, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.66 (qu, J = 7 Hz, 2H), 2.04 (q, J = 7 Hz, 2H), 2.58(t, J = 7Hz, 2H), 3.58 (s, 2H), 5.0 (m, 2H), 5.72 (m, 1H), 7.28 (m, 3H), 7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.2, 33.0, 36.1, 40.0, 115.2, 127.9, 129.1, 129.3, 133.3, 137.9, 205.3; exact mass, m/z 268.0367 (calcd for $C_{13}H_{16}OSe$, m/z 268.0366). Anal. Calcd for $C_{13}H_{16}OSe$: C, 58.43; H, 6.03.

Found: C, 58.33; H, 6.05.

Cyclization of 321 with Triphenylstannane.

The general procedure for radical cyclization (p.137) was followed using **321** (0.116 g, 0.434 mmol) in benzene (20 mL), triphenylstannane (0.14 mL, 0.55 mmol) in benzene (10 mL), AIBN (0.0150 g, 0.09 mmol) in benzene (10 mL) and an addition period of 13.5 h. After a further 1.5 h the majority of the benzene was removed by distillation at atmospheric pressure using a 10 cm Vigreux column. The residue was redissolved in benzene, placed in to a volumetric flask (5 mL) and made up with benzene. VPC analysis (OV-1, 140°C) showed two major products; cycloheptanone (ret. time 2.20 min) and 3-methylcyclhexanone (ret. time 1.75 min). Five calibration standards each containing approximately equal weights (5 to 45 mg) of cycloheptanone (Aldrich) and 3-methylcyclohexanone (Aldrich) were made up with benzene to 5 mL. Using these standards the yields of cycloheptanone and 3-methylcyclohexanone were determined as (19.9±0.3 mg, 40.9±0.6%) and (21.9±0.4 mg, 45.0±0.8%) respectively. The yield of the 6-hepten-2-one was based upon peak area comparison with cycloheptanone and 3-methylcyclohexanone in the reaction mixture and was thus calculated in *both cases* as (1.8 mg, 3.7%). GCMS analysis identified the two major products as cycloheptanone and 3-methylcyclohexanone.

6-Hepten-2-one

A mixture of methyl 3-oxo-7-octenoate **308** (5.05 g, 29.7 mmol) and 5% aqueous sodium hydroxide (60 mL) was refluxed for 3 h. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). Fractional distillation yielded 6-hepten-2-one [2.20 g, 66.0%, bp 73-74°C 55 mm (Lit. bp 73-75°C, 50 mm)] as a clear colorless liquid (>98.5% pure by VPC, OV-I, 120°C): IR (CCl_4 cast) 1718, 1640, 1360, 910: ^1H NMR (200 MHz, $CDCl_3$) δ 1.70 (qu, J = 7 Hz, 2H), 2.10 (q, J = 7 Hz, 2H), 2.20 (s, 3H), 2.48 (t, J = 7 Hz, 2H), 4.95-5.10 (m, 2H), 5.80 (m, 1H).

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